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British Heart Journal

A monthly journal of cardiology published in association with the British Cardiac Society

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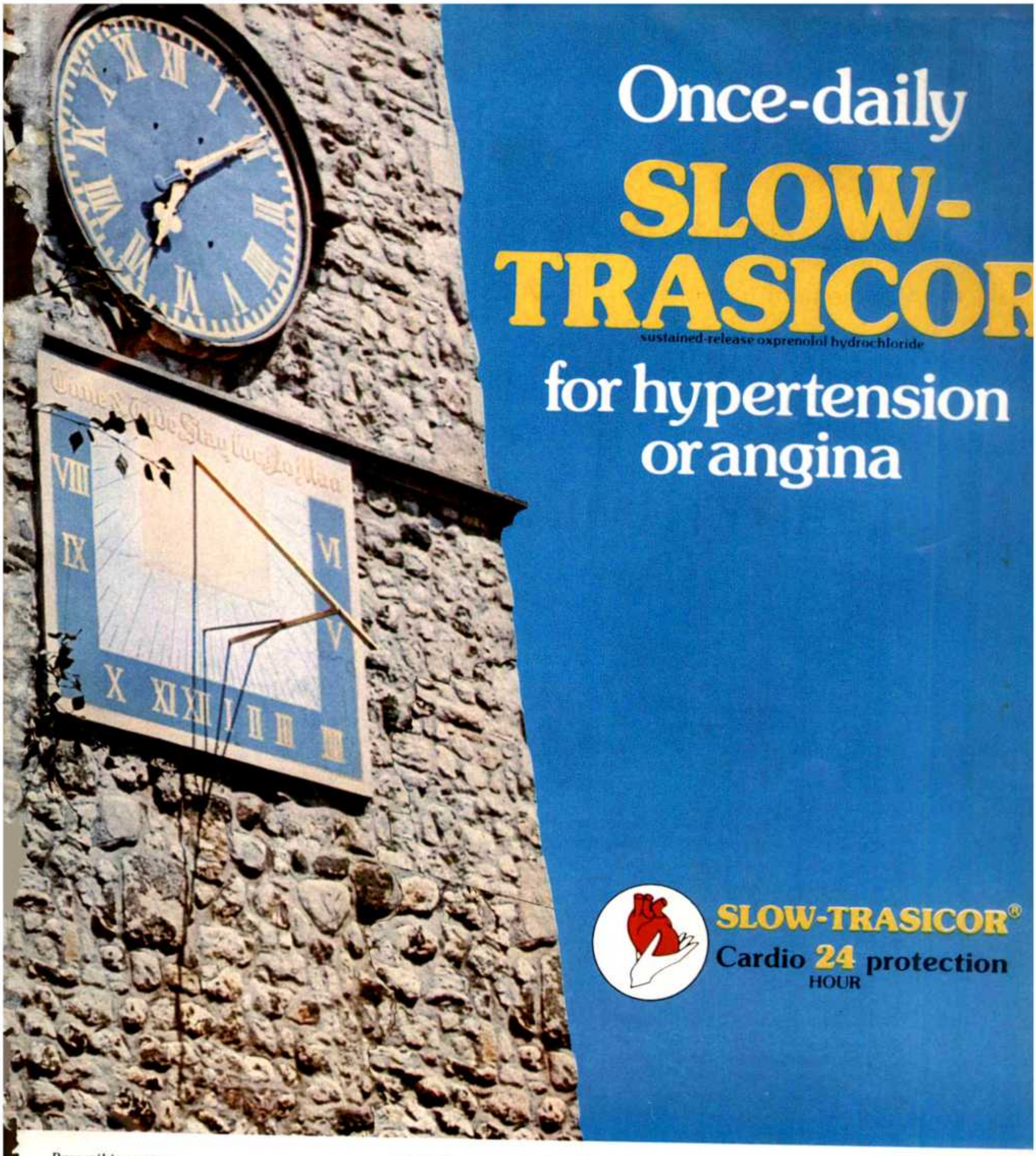
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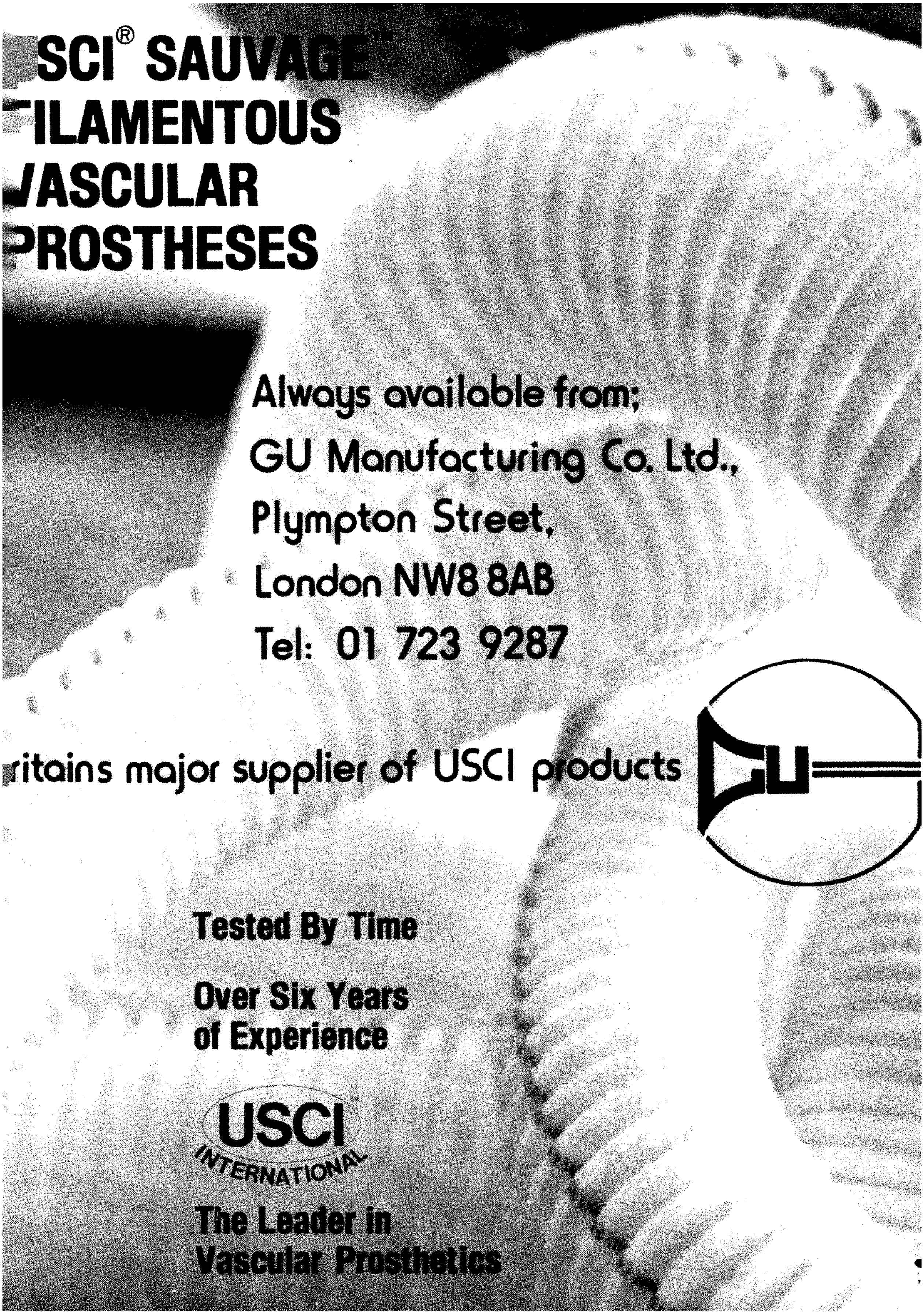

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4. Circulation, 1975, 51 & 52, Suppl. II, 147 5. Lancet, 1975, i, 1257 6. Circulation, 1975, 51 & 52, Suppl. II, 199

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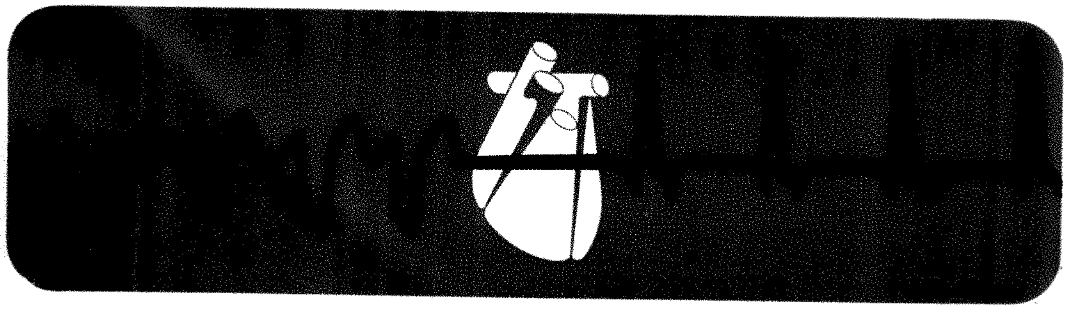

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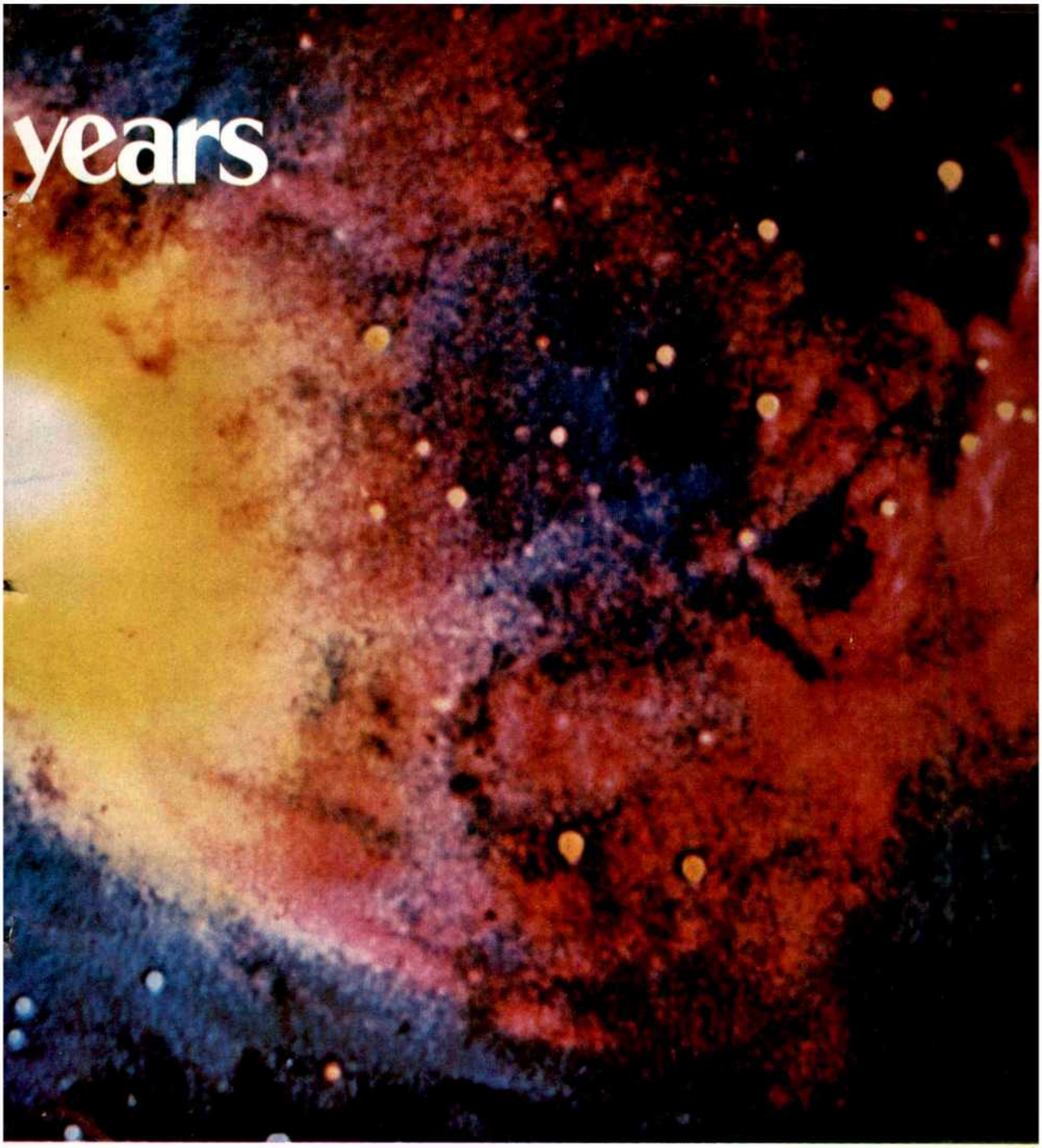

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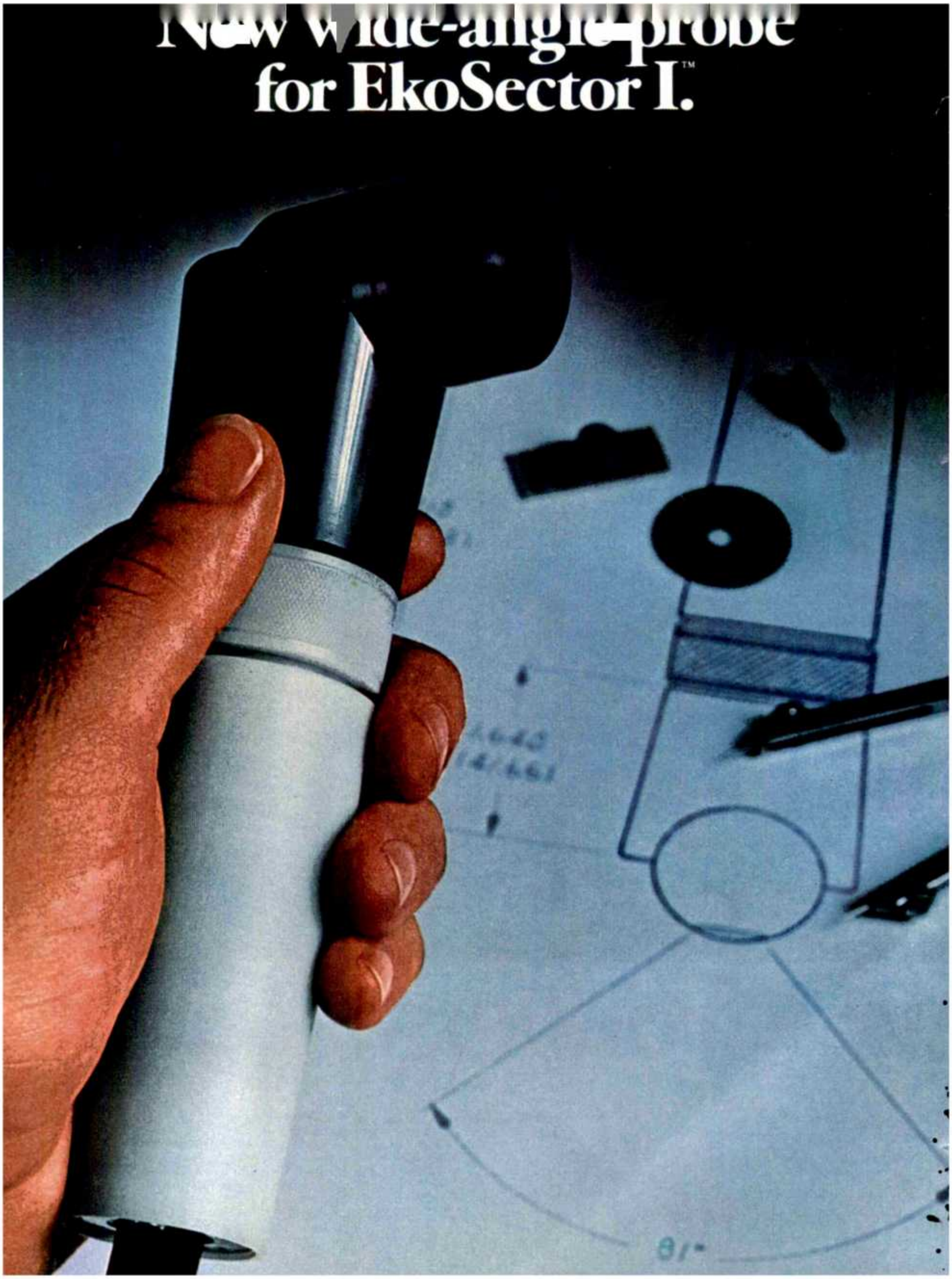

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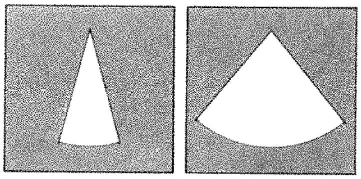

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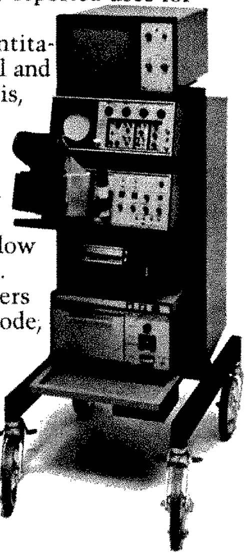

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2. JAMA (1972). *222*:676.
3. New Zealand J. Med. (1972). *76*:12.

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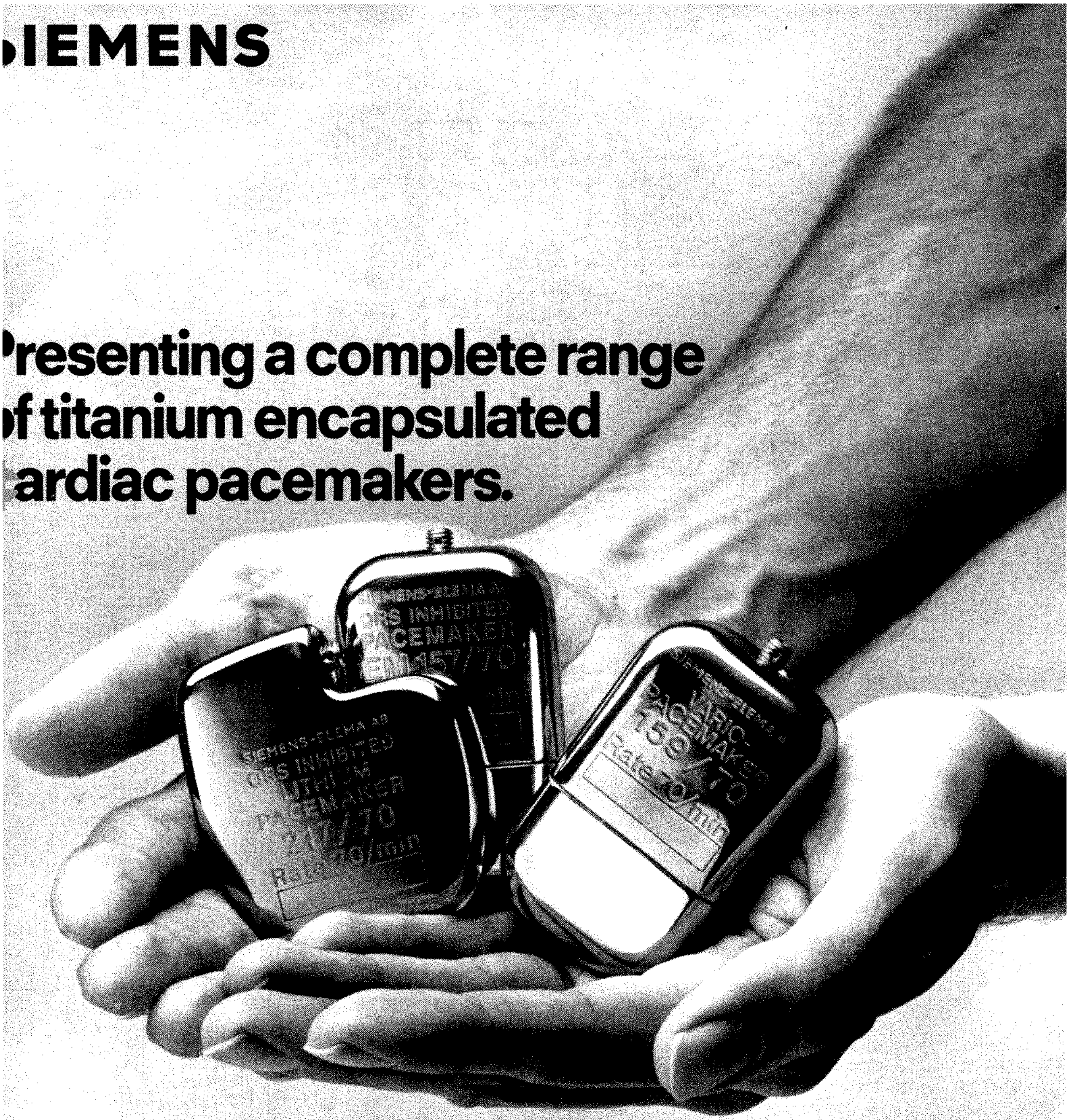

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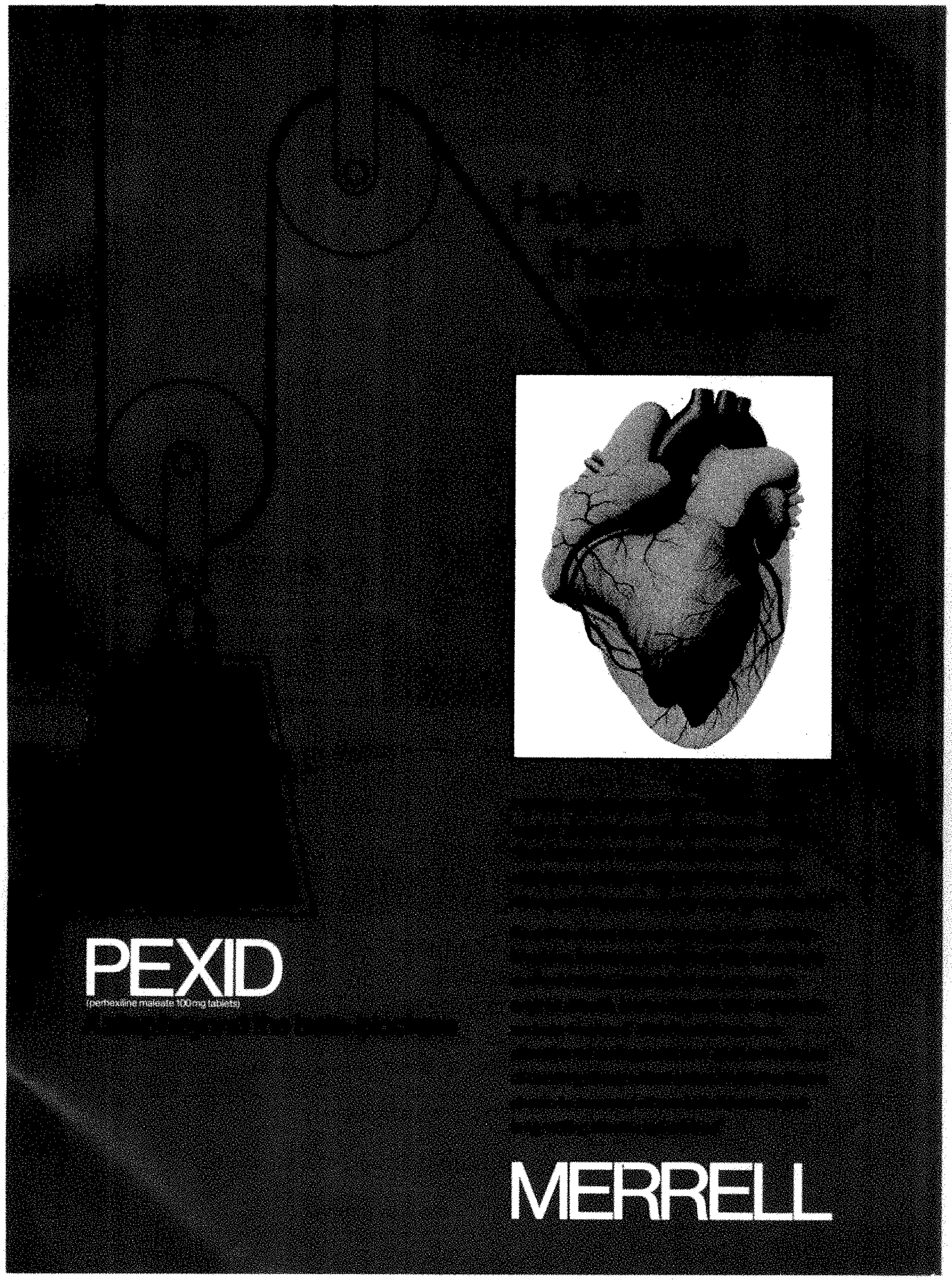

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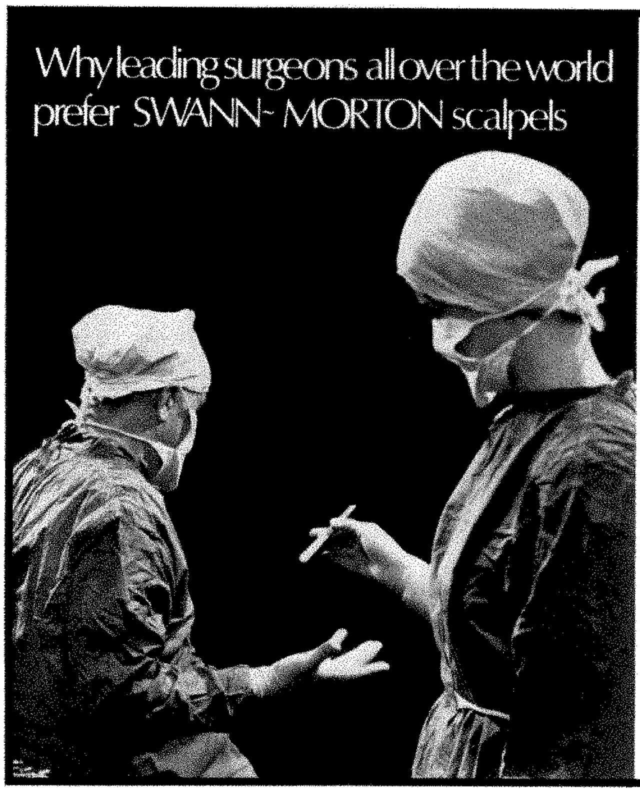
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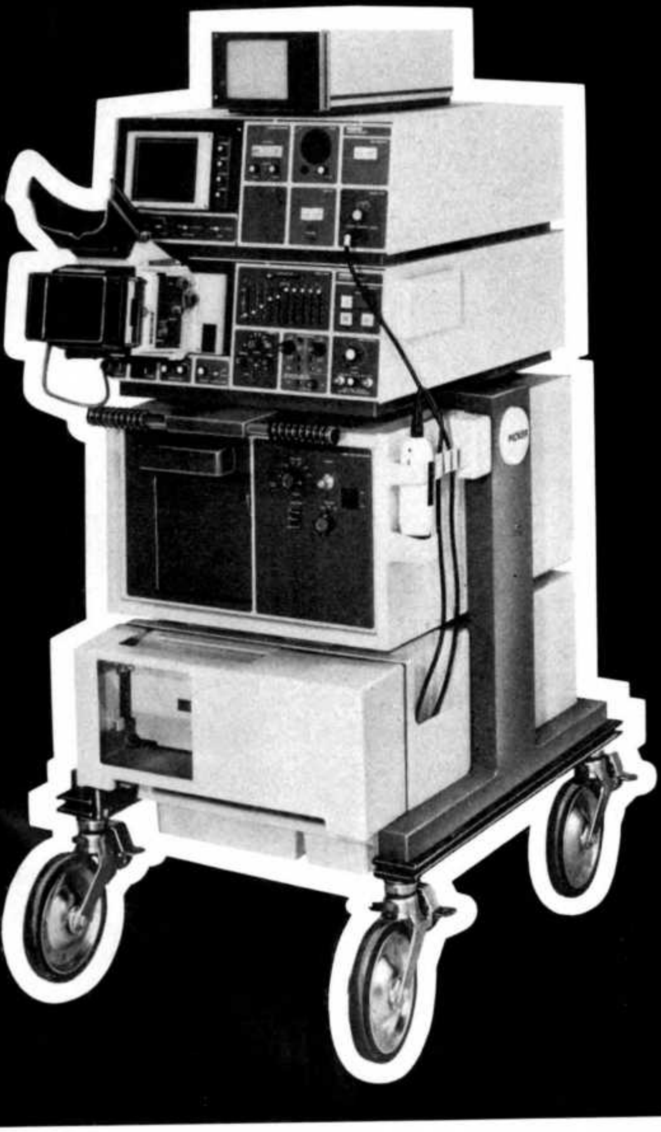

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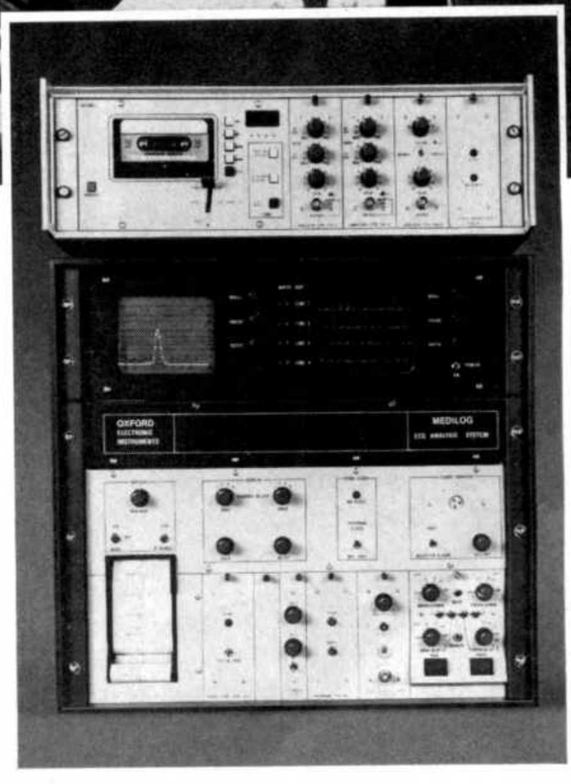

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References

1. *Br.J.Anaesth.* (1977) **49**, 251
2. *Acta.anaesth.belg.* (1976) **27**, suppl. 134
3. Data on file, Reckitt & Colman Limited
4. *Arch.gen.Psychiat.*, accepted for publication

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1. Decalmer, P. B. S. *et al* 1977, *Acta Therapeutica*, **3**, 99.

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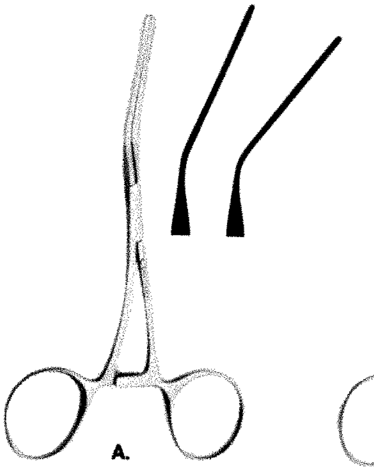

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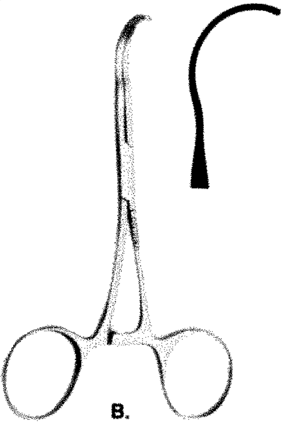

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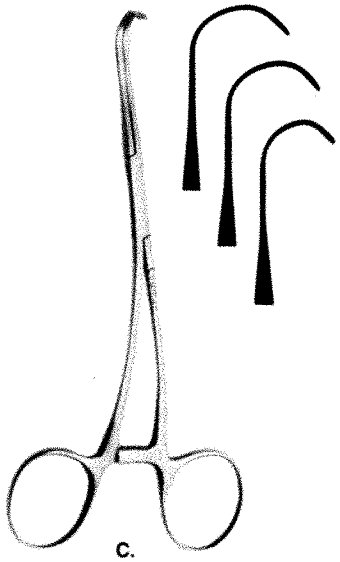

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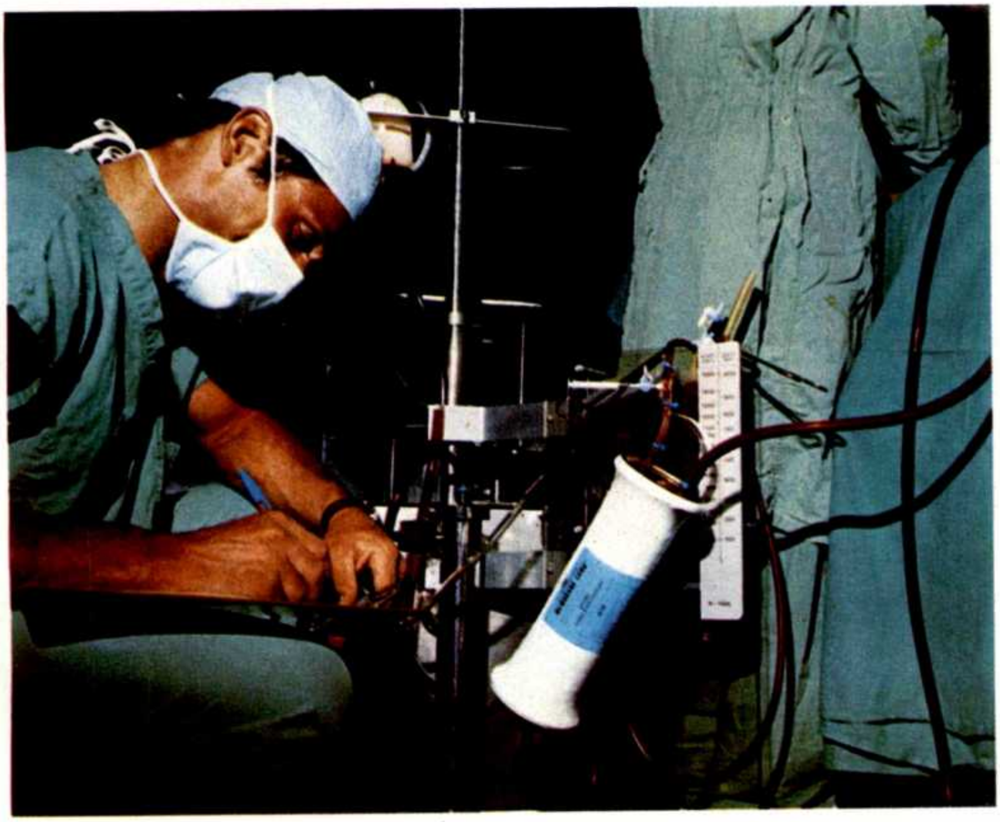

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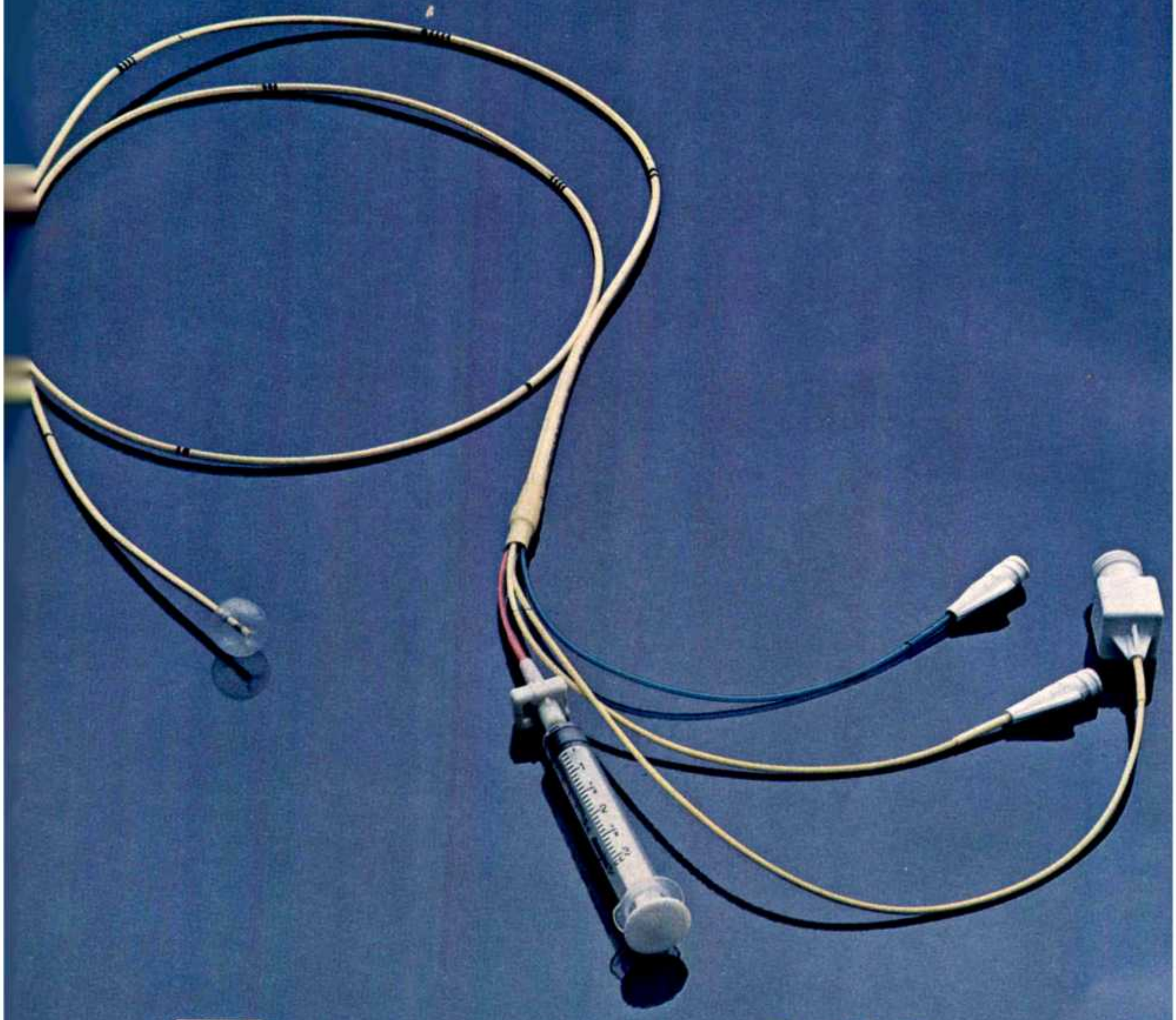

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British Heart Journal, 1978, **40**, 941-950

The diagnosis of a non-stenotic bicuspid aortic valve

GRAHAM LEECH, PETER MILLS, AND AUBREY LEATHAM

From The Cardiac Department, St George's Hospital, Hyde Park Corner, London

SUMMARY Follow-up of a group of subjects in whom an aortic ejection sound was the only abnormal finding revealed a bicuspid aortic valve at necropsy or operation in 6 cases. High speed echophonocardiographic studies in 15 subjects with aortic stenosis and known to have bicuspid valves, showed the ejection sound to be exactly synchronous with final halting of the opening aortic valve cusps. Echocardiographic visualisation of the aortic valve from the apex, looking up the left ventricular outflow tract, showed valve echoes during systole indicating abnormal cusp configuration. This proved a more sensitive indicator of a bicuspid aortic valve than the finding of an eccentric aortic valve closure line.

These findings were used to evaluate 37 subjects with the auscultatory finding of an isolated aortic ejection sound and the diagnosis of a non-stenotic bicuspid aortic valve was confirmed in 30. The usual cause of misdiagnosis was a sound associated with late tricuspid valve closure.

The auscultatory finding of an aortic ejection sound, in the absence of other signs of aortic stenosis, indicates a non-stenotic, bicuspid aortic valve. Confirmation of aortic valvar origin of the sound can be provided by a simultaneous echophonocardiogram.

The observation that an early systolic sound might be associated with an abnormal aortic valve was first noted by Lian and Welti (1937), and in 1940 Wolferth and Margolies suggested that this sound could be regarded as an 'opening click' of a diseased aortic valve. Leatham and Vogelpoel (1954) described it as an 'aortic ejection sound', and showed that it occurred approximately at the time of the carotid upstroke. Cineangiographic studies by Epstein *et al.* (1965) subsequently disclosed that in aortic valve stenosis the ejection sound coincided with the halting of the upward 'doming' movement of the fused aortic valve cusps. It is now generally accepted that in patients with obstruction to left ventricular outflow, an ejection sound indicates the presence of aortic valve stenosis with valve cusps that are reasonably mobile and not heavily calcified (Hancock, 1961; Oakley and Hallidie-Smith, 1967; Glancy and Epstein, 1971).

It has, however, been noted that an early systolic sound may occur in patients in whom there is no detectable degree of aortic stenosis (Leatham *et al.*, 1963). In view of the observation that a non-stenotic bicuspid aortic valve is a common congenital anomaly of the heart (Wauchope, 1928), we suggested that this might be the origin of the early systolic sound in these patients.

Received for publication 19 October 1977

The present study was designed to examine this hypothesis and to develop criteria for the non-invasive recognition of a bicuspid aortic valve. Combined echo- and phonocardiography offers a non-invasive method for studying the motion of cardiac valves and their associated sounds. This can be used, in a manner analogous to the cineangiographic techniques of Epstein *et al.* (1965), to identify the aortic valve as the origin of a suspected aortic ejection sound.

Subjects and methods

PATIENTS

All the patients in this study had an early systolic sound approximately synchronous with the beginning of the external carotid pulse upstroke. None had evidence of any abnormality apart from the aortic valve. No patient had systemic hypertension or rheumatic heart disease.

Group 1 consisted of 6 patients in whom an isolated aortic ejection sound, documented phonocardiographically, was subsequently shown to have been associated with a bicuspid aortic valve. In 4 patients, a non-stenotic bicuspid aortic valve was found at necropsy. The other 2 patients developed aortic stenosis, and at operation a calcified, congenitally bicuspid aortic valve was found.

Group 2: The echocardiographic feaures of a bicuspid aortic valve and the timing relation between valve motion and the associated ejection sound were studied in 15 patients with aortic stenosis. Of these, 10 had undergone surgery; in each case the valve had been found to be bicuspid, but its anatomy was not altered by the procedure, which was either a limited valvotomy or debridement. In the remaining 5, the diagnosis of a bicuspid aortic valve had been established unequivocally by angiography.

Group 3 comprised 37 patients referred for cardiac assessment, in whom an early systolic sound, thought to be an ejection sound, was noted on auscultation. There was no evidence of aortic stenosis and the chest *x*-ray film and electrocardiogram were normal.

As *controls* 30 subjects without any evidence of cardiac abnormality were studied.

METHODS

A commercial echoscope[1] with 2·25 MHz focused transducer was modified to increase the pulse repetition rate from 1000 to 2000/s. The output was coupled via a shift register interface to a 6-channel oscilloscopic strip chart recorder,[2] allowing simultaneous recording of M-mode echo, two phonos, electrocardiogram, external carotid pulse, and respiration. The recorder resolution was improved by doubling the echo depth magnification and increasing the paper speed to 200 mm/s. This system is capable of resolving tissue depths to 0·5 mm and time intervals to ±2·5 ms. Registration delay between channels (including echo) is negligible (less than 0·3 ms).

The following studies were performed on all patients, except 5 of the 6 in group 1 who were seen before echocardiography was available.

(1) A routine echocardiogram.

(2) High speed echophonocardiograms (Leatham and Leech, 1975) to define the relation between mitral and tricuspid valve closure, aortic and pulmonary valve opening, and the heart sounds recorded at the pulmonary area and left sternal border. Recordings of each valve were made after the patient had achieved a steady resting state and a regular heart rate.

(3) The aortic valve was also visualised, with the transducer placed over the cardiac apex. The ultrasound beam was directed medially and cephalad towards the mid-point of the right clavicle, to locate the mitral valve. From this point, the aortic valve was located by angling still more medially and cephalad. The appearance of the aortic valve in this view is similar to that of the pulmonary valve from the third left intercostal space. These recordings will be referred to as apical aortic valve echocardiograms.

Standard high frequency phonocardiograms were recorded from two chest sites simultaneously (pulmonary area and apex, followed by aortic area and left sternal border), together with the indirect carotid pulse using a small funnel pickup, respiration phase, and electrocardiogram. From these recordings, the following measurements were made:

(a) The time interval from the onset of the high frequency vibrations of the first heart sound to the onset of the ejection sound.

(b) The relative amplitudes of the first sound, ejection sound, and second sound at the apex, in all phases of the respiratory cycle.

(c) The relation between the ejection sound and the onset of the external carotid pulse upstroke.

(d) Carotid pulse tracings were used to measure the 'T-time', that is time to half maximal upstroke excursion (Epstein and Coulshed, 1964), and left ventricular ejection time (Weissler *et al.*, 1968).

Results

The measurements are summarised in the Table and are discussed below.

GROUP 1

Phonocardiograms had previously been recorded on the 6 patients subsequently shown at necropsy or surgery to have a bicuspid aortic valve. Fig. 1 illustrates the features of the early systolic sound seen in these patients. It is a high frequency sound, occurring 45 to 62 (mean 55) ms after the onset of the first heart sound, and shortly before the upstroke of the indirect carotid pulse. Recordings at the apex showed that the sound was usually as loud as the first heart sound and its intensity did not vary with respiration. The aortic component of the second sound was louder than normal, averaging 3·5 times the amplitude of the first sound, compared with a ratio of 2·0 in the controls. In the only case in whom echocardiographic studies were performed, the sound started exactly at the moment of halting of the opening aortic valve cusps. Five of the six had a systolic murmur graded from 1 to 2/6, but none had clinical evidence of aortic stenosis. Carotid 'T-time' and left ventricular ejection time indices were within normal limits in each patient.

GROUP 2

Each of the 15 patients in group 2, known to have a stenotic bicuspid aortic valve, had an ejection

---

[1] Smith Kline Instrument Co. Ekoline 20.

[2] Cambridge Medical Instruments Model 72112.

Table *Summary of results*

Measurement		*Group 2: bicuspid valve and stenosis (n = 15)*	*Group 3: bicuspid valve no stenosis (n = 30)*	*Normal: controls (n = 30)*
SI onset to ejection sound or halting of opening aortic cusps (mean ± SD)		48 ± 11 ms (n = 13)	64 ± 12 ms	61 ± 13 ms
Ejection sound/SI loudness ratio at apex	⩾2:1	9	11	N/A
	> 1:1	2	19	
A2/SI loudness ratio at apex	⩾2:1	10	21	11
	> 1:1	12	29	21
Systolic ejection murmur	None	0	2	23
	< 3/6	0	28	7
	⩾3/6	15	0	0
Appearance of aortic valve diastolic echoes	Multiple	9	7	0
	Calcified	2	0	0
Aortic valve 'eccentricity index'	> 1·5	8	14	0
	1·25-1·5	2	8	0
	< 1·25	3	8	30
Systolic separation of aortic cusps as percentage of lumen diameter (mean ± SD)		82 ± 13% (n = 13)	81 ± 10%	74 ± 8%
Apical view of aortic valve	Visualised/attempted	12/14	26/30	28/30
	systolic echo seen	12	26	0

sound 30 to 65 (mean 48) ms after the onset of the first sound. Echophonocardiographic studies showed that the onset of the ejection sound coincided with halting of the opening movement of the aortic valve cusps in the conventional view and in the apical view (Fig. 2). In each patient, both the mitral and tricuspid valves had closed, and the pulmonary valve had opened, before maximal aortic valve opening. Evaluation of the aortic valve echoes in diastole was not possible in two patients, who had multiple dense echoes in the aortic root suggesting the presence of calcium and precluding further measurements. Of the remaining 13 patients with proven bicuspid valves, the 'eccentricity index' of

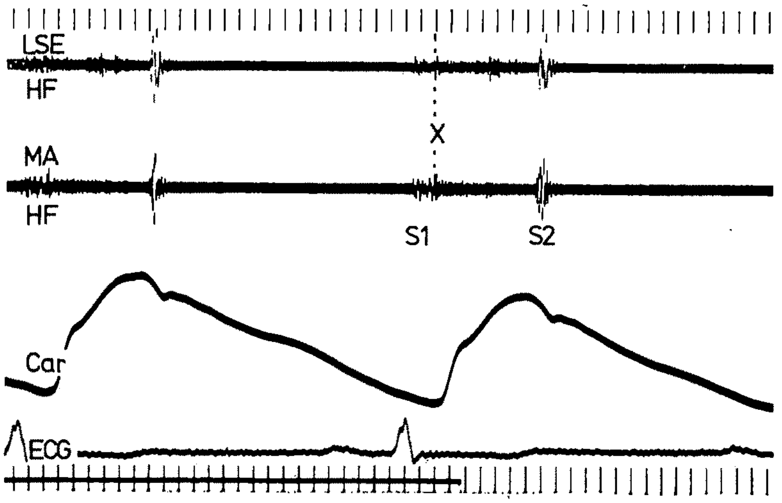

Fig. 1 *Phonocardiogram showing high frequency sound tracings recorded at left sternal edge (LSE) and mitral area (MA), with carotid pulse (Car) and electrocardiogram (ECG), recorded in 1962. The patient had an early systolic sound (X), thought from its relation to the carotid pulse upstroke to be an aortic ejection sound. He subsequently died of myocardial infarction and was shown at necropsy to have a non-stenotic bicuspid aortic valve. HF, high frequency; S1, first sound; S2, second sound.*

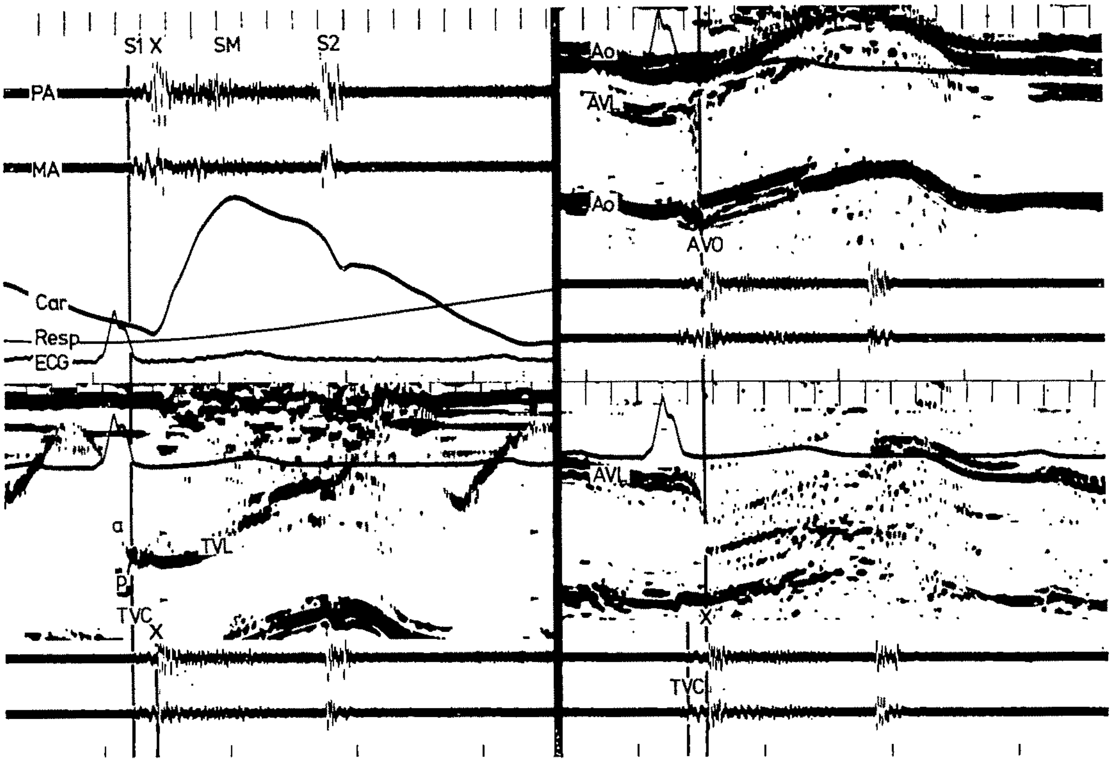

Fig. 2 *Selection of recordings from a patient in group 2 with a surgically proven bicuspid valve.* Top left: *phonocardiogram showing ejection sound (X) and systolic murmur (SM); the carotid pulse upstroke is slow.* Lower left: *echo recording of tricuspid valve leaflets (TVL), showing closure (TVC) at apposition of anterior (a) and posterior (p) leaflets, occurring well before the ejection sound.* Top right: *conventional aortic valve echo showing closed leaflets (AVL) anteriorly displaced within the aortic lumen (Ao). Onset of the ejection sound vibrations coincides precisely with halting of the opening of the valve (AVO).* Lower right: *apical view, showing valve echoes during systole and relationship of opening to ejection sound. All recordings at 200 mm/s. Time lines 40 ms.*

the aortic valve echo during diastole (Nanda *et al.*, 1974) was greater than 1·5 in 8 patients and greater than 1·25 in 2 more. In the other 3 patients, however, the eccentricity index was below 1·25 and the overall appearance of the valve from the conventional transducer position was normal. Visualisation of the aortic valve from the apex was successful in 12 cases. In each instance, the aortic cusp echoes were recorded during most of systole, suggesting that part of the cusp structure remained in the central portion of the lumen of the aorta during ejection (Fig. 2 lower right panel), an appearance never found in the control group.

GROUP 3

Thirty-seven patients thought on auscultation to have an aortic ejection sound were studied using the same techniques. In 30 of these patients, the onset of the sound coincided with maximal aortic valve opening, confirming the clinical impression of an aortic ejection sound (Fig. 3). The interval from the onset of the first heart sound to the ejection sound and maximal aortic valve opening was 43 to 91 (mean 64) ms. This was essentially the same as the interval from the first sound onset to maximal aortic opening in the normal control group, and highly significantly ($P < 0{\cdot}001$) longer than in the group 2 patients with aortic stenosis. In 19/30 the ejection sound was louder than the first sound at the apex, and in the majority, the aortic component of the second sound was accentuated. A soft systolic murmur was present in 28, and a very soft early diastolic murmur in 4 cases. Carotid pulse 'T-time' and left ventricular ejection time indices were normal (except in one case of unoperated coarctation of the aorta) and there was no clinical evidence of aortic stenosis.

The aortic valve eccentricity index exceeded 1·5

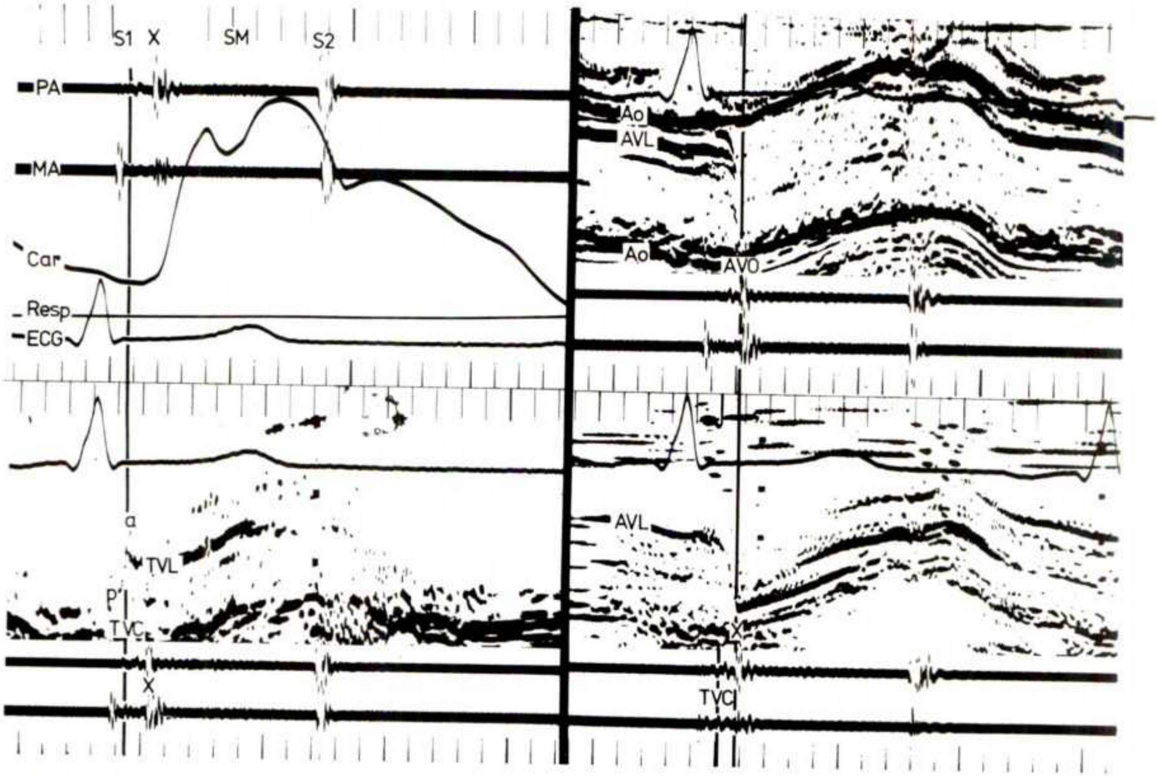

Fig. 3 *Recordings from a patient in group 3 arranged in the same way as Fig. 2. Note the similarity, apart from the minimal murmur and normal carotid rise time, suggesting no stenosis.*

in 14 cases, was between 1·5 and 1·25 in 8, but was less than 1·25 in 8 of the 30 cases. Multiple diastolic echoes were found in 7 patients. In none was there evidence of aortic valve calcification. The initial separation of the aortic cusp echoes at the beginning of ejection, expressed as a percentage of the aortic lumen diameter, was significantly greater ($P < 0·01$) in groups 2 and 3 than in the normal controls. The aortic valve was successfully visualised from the apex in 26 of these 30 cases and in every instance valve echoes could be seen during systole.

In the remaining 7 patients in group 3, the sound thought on auscultation to be an aortic ejection sound did not coincide with maximal aortic valve opening. In 5, it coincided with tricuspid valve closure and preceded maximal aortic opening (Fig. 4). Moreover, its intensity increased on inspiration and it was best heard at the lower left sternal border. In one of these, the tricuspid component was very late and loud and the electrocardiogram was compatible with a mild form of Ebstein's anomaly; in another, with a moderately loud systolic murmur, there were echocardiographic signs suggestive of discrete subvalvar aortic obstruction; the other 3 had relatively widely split first heart sounds (up to 40 ms), but without any electrocardiographic evidence of conduction delay. In the remaining 2 of the 7 patients, the ejection sound was shown to coincide with maximal pulmonary valve opening, its intensity diminished on inspiration, and the pulmonary component of the second heart sound was delayed, suggesting mild pulmonary valve stenosis. In none of these patients was the aortic valve echo seen during systole in the apical view, nor were eccentric or multiple diastolic echoes seen in the conventional aortic valve echocardiogram.

CONTROLS

None of the 30 patients without evidence of cardiac disease had a sound coinciding with maximal aortic valve opening. Echocardiographically, the eccentricity index of aortic valve closure was always less than 1·25 and the aortic cusps were never recorded during systole in the apical view.

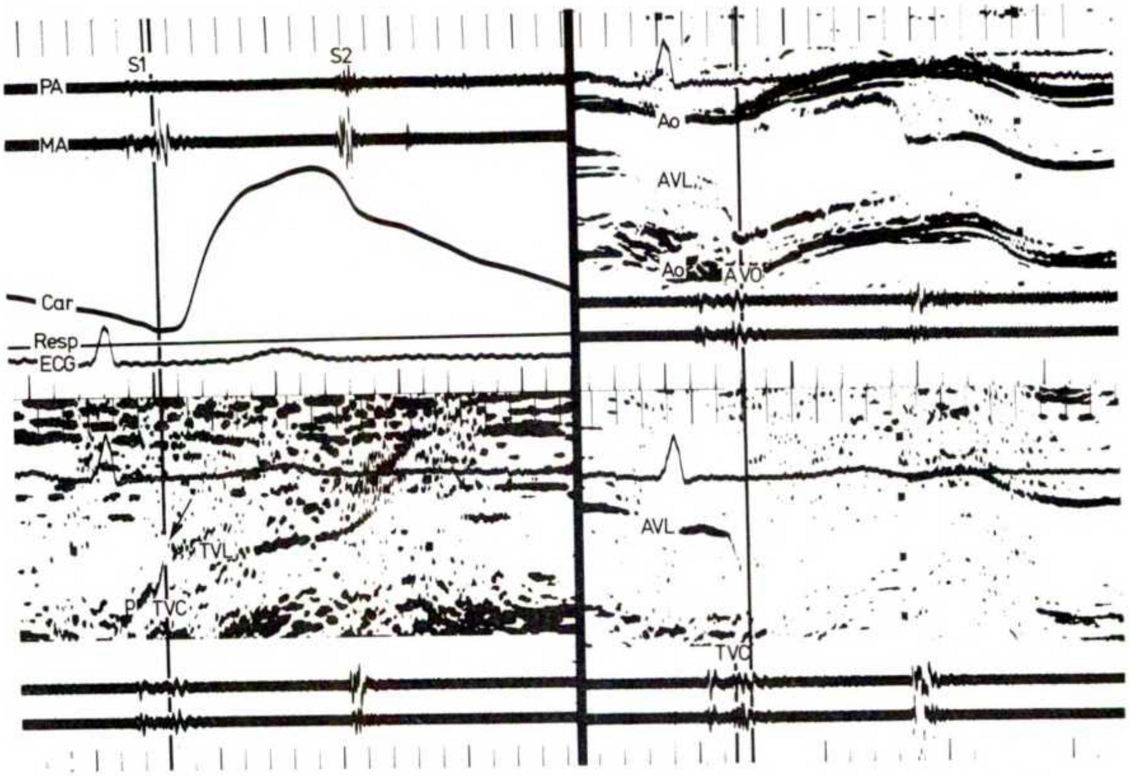

Fig. 4 *Recordings from a group 3 patient mistakenly thought on auscultation to have an aortic ejection sound, arranged as in Figs 2 and 3. The phonocardiogram is very similar, except that the sound precedes the carotid upstroke by 40 ms, and is shown to coincide with tricuspid closure* (arrowed), *even though there is no ECG evidence of conduction delay. The aortic valve echoes are normal, both in the conventional and apical views, and maximal valve opening does not occur until after the suspect sound.*

Discussion

Our aim has been to employ the non-invasive techniques of echo- and phonocardiography to establish diagnostic criteria for a non-stenotic, bicuspid aortic valve. Aortic ejection sounds are a feature of aortic valve stenosis, but one of us (A.L.) had noted that these sounds might also be heard in patients without clinically detectable aortic valve obstruction. Epstein *et al.* (1965) had shown that the ejection sound in aortic stenosis is caused by halting of the upward motion of the stiffened, fused valve cusps. It seemed likely that a valve with only two cusps, which could not fold completely against the aortic wall during ejection, might behave in a similar manner, and so it was postulated that an aortic ejection sound, in the absence of aortic stenosis or regurgitation, might be a sign of an uncomplicated bicuspid valve. Patients with this sign were, therefore, followed up, and unequivocal evidence of the presence of a bicuspid valve was obtained in 6 cases (group 1).

Since a bicuspid aortic valve is a relatively benign abnormality and the patients with an isolated ejection sound were asymptomatic, the use of cardiac catheterisation and angiography to confirm the diagnosis could not be justified. However, the technique of simultaneous high speed echo- and phonocardiography (Leatham and Leech, 1975), using a recording paper speed of 200 mm/s and corresponding electronic magnification of the echocardiographic image, can identify accurately the origin of cardiac sounds.

It is important to appreciate that the timing of a transient mechanical event such as a valve tensing after opening or closing is indicated by the *onset* of the associated sound; the quality and duration of the sound vibrations depend on the elasticity and damping of the vibrating structures, and the appearance of the sound on the phonocardiogram is influenced by the type of electronic filtration employed in the amplifier. An analogous situation occurs when a hammer strikes a bell: the sound *begins* at the moment of impact, but the pitch of the note depends on the size of the bell, and its duration on the amount of damping present.

By recording the motions of all 4 cardiac valves, it is possible in most subjects to demonstrate a unique association between each high frequency sound and halting of the motion of one of the valves. In the case of an aortic ejection sound, the mitral and tricuspid valves have already closed and, with occasional exceptions, the pulmonary valve has already opened fully before the aortic cusps reach their maximal opening separation. There were only two instances in this study when another valve opened or closed so close to aortic opening as to make it difficult to be sure with which valve an early systolic sound was associated. It was an invariable finding that the onset of the vibrations of the ejection sound recorded in the patients with aortic stenosis was precisely coincident with the moment of final halting of the opening aortic valve cusps. These findings are similar to those of Waider and Craige (1975). Gamboa *et al.* (1964) investigated the timing of the ejection sound in semilunar valve stenosis. In pulmonary stenosis, they found a good relation between the severity of the stenosis and the interval from the QRS onset on the electrocardiogram to the ejection sound, but they could not show a similar relation in aortic stenosis. Using high-speed recordings, and eliminating variations in electromechanical delay by timing from the component of the first heart sound shown by echophonocardiography to be mitral closure, we have found that maximal aortic valve opening occurs significantly earlier ($P < 0{\cdot}005$) in patients with a degree of stenosis, compared with normals and those with non-stenotic bicuspid valves. Though the time intervals are short, it is possible that this may provide a basis for the echophonocardiographic assessment of the severity of aortic stenosis.

Most of the group 3 patients had a soft ejection systolic murmur, this generally being the reason for their referral by the family or school doctor. In the 2 cases without a murmur, the ejection sound had been detected by one of us during a routine examination. Though the non-invasive assessment of the severity of aortic stenosis is often unreliable, we were able to show abnormal 'T-time' and ejection time indices in all the 5 patients in group 2 who had been shown by catheterisation to have valve gradients of 2·7 to 6·7 kPa (20 to 50 mmHg). Using the same criteria, all the measurements in group 3, except one case with coarctation, were normal. Furthermore, none had electrocardiographic or echo evidence of left ventricular hypertrophy. Thus, despite the murmur, we do not believe the group 3 patients have significant aortic stenosis. (Of the 30 normal controls, 7 also had an audible systolic murmur.)

The intensity of the second heart sound is greater in patients with bicuspid valves than normals. The increased area of the large cusp, which is responsible for the ejection sound when it opens, also makes a loud noise when it tensions as it halts after closing.

The echocardiographic features of a bicuspid aortic valve have been described previously. Our findings support the observations of Nanda *et al.* (1974) that a bicuspid aortic valve is characterised by an eccentric closure line and multiple diastolic echoes. However, as Radford *et al.* (1976) emphasised, this is not invariably the case. Ten proven bicuspid valves had an 'eccentricity index' (aortic lumen diameter divided by twice the minimum diastolic closure line—aortic wall distance) greater than 1·25, but in 3 it was within the normal range of under 1·25. Of the 30 group 3 patients thought to have bicuspid valves, 8 had eccentricity indices under 1·25, and 6 of the 8 did not have multiple echoes either. Thus, conventional echo studies would fail to detect the bicuspid valve in 11 out of 43 of our cases, and the presence of an aortic ejection sound defined by echophonocardiographic studies is a more sensitive diagnostic feature.

In those cases where the closure line was eccentric it was invariably displaced anteriorly within the aortic lumen. This is surprising in view of the findings of Roberts (1970), who found considerable variation in the anatomical configuration of 59 necropsy cases of bicuspid aortic valves.

At first sight, it is paradoxical that a bicuspid valve appears on echo recordings to open wider than a normal valve. Inability of the cusps to fold back parallel to the wall of the aorta causes them to bulge outwards, increasing their separation as seen by the ultrasound beam traversing the aortic root.

It has been our practice to study Starr-Edwards aortic prostheses by placing the echo transducer over the point of maximal apical pulsation and directing the ultrasound beam up the aortic outflow tract to detect the ball motion, which is parallel to the axis of the aorta. A feature of a bicuspid aortic valve is that, unlike a normal valve, the cusps cannot fold away from the centre of the aortic lumen during ejection. This leads to the 'domed' appearance on angiograms. We thought the apical view might make it possible to detect this echocardiographically. The aortic valve was recorded successfully in 66 cases, which was 88 per cent of those in whom it was attempted. Proof that we were recording the aortic valve was provided by the identical timing of the opening and closing phases of its motion

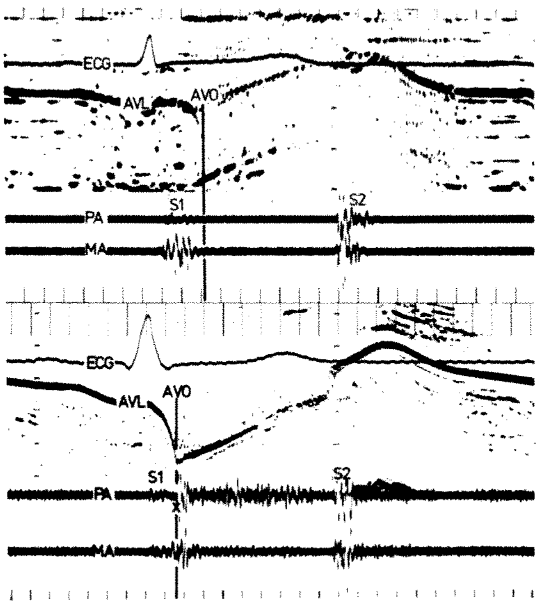

Fig. 5 *Apical aortic valve echo in a normal subject (top) and a patient with a surgically demonstrated bicuspid aortic valve (bottom). Cusp echoes are seen during systole in the lower trace, and maximal valve opening coincides with the onset of the ejection sound.*

when compared with the conventional view. In addition, its relation to the mitral valve and the similarity of the tracing to that of the pulmonary valve when seen from the third intercostal space (i.e. from the same relative angle) helped identification during the study.

In patients with proven bicuspid valves (group 2), echoes from the aortic valve cusps remained visible during systole. In contrast, cusp echoes were not detected during systole in the normal controls (Fig. 5). The presence of valve echoes during systole suggests only that the cusps cannot fold completely parallel to the aortic wall, and this appearance is, therefore, also seen in congenital aortic valve stenosis with a tricuspid or unicuspid valve, and in rheumatic aortic stenosis. In addition in patients with low stroke output, for example in dilated cardiomyopathy or ischaemic disease, incomplete aortic valve opening sometimes produces 'fluttering' echoes during systole. However, with these exceptions, we believe that detection of aortic cusp echoes during systole in the apical view is a sign of a bicuspid aortic valve.

An aortic ejection sound (Fig. 6) is recognised clinically as an early systolic sound, giving the impression of wide splitting of the first heart sound. The following features are helpful in making the diagnosis on auscultation; (a) it is a loud sound and its intensity does not vary with respiration; (b) it is heard over the whole praecordium, but its relation to the first sound, and thus the impression of 'wide splitting of the first sound', is best obtained at the apex, whereas true splitting of the first sound is most obvious at the lower left sternal edge; and (c) the aortic component of the second heart sound is usually loud.

Even so, it is possible to be mistaken. Analysis of our recordings leads us to conclude that 7 of the 37 patients originally thought to have bicuspid aortic valves do not in fact have an aortic ejection sound. The commonest error was to mistake wide physiological splitting of the first sound for an aortic ejection sound. An atrial sound preceding the first sound may cause difficulties, but it is of much lower frequency and usually varies with respiration. With physiological splitting of the

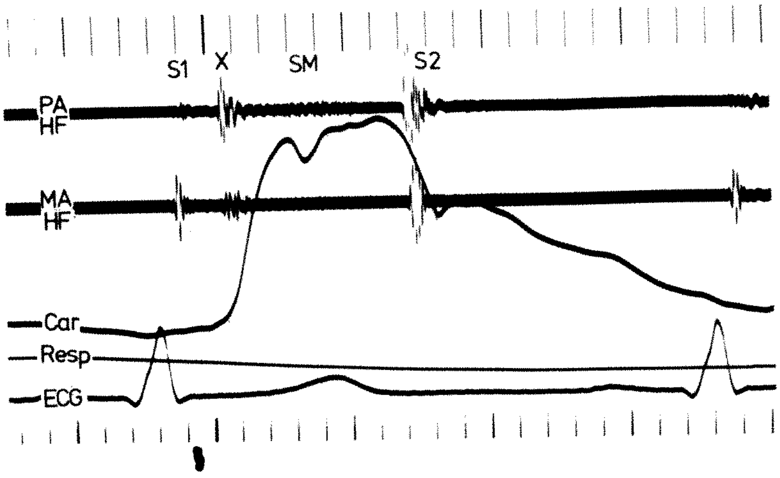

Fig. 6 *Auscultatory features of an aortic ejection sound. Note the timing relative to the carotid upstroke, the soft systolic murmur and the loud second sound.*

first sound, the gap is usually narrower, but great difficulty may be encountered in right bundle-branch block, since the timing of the delayed tricuspid closure sound may be identical to an aortic ejection sound and if it is loud, as in atrial septal defect, the two may be indistinguishable.

Ejection sounds associated with pulmonary hypertension may be difficult to distinguish from aortic ejection sounds, since with raised pulmonary artery pressure ejection is delayed and the timing is similar to that of a left-sided sound (identical in the case of Eisenmenger ventricular septal defect). Unlike pulmonary stenosis, there is little variation in amplitude with respiration since atrial contraction cannot partially raise the valve in the face of high pulmonary artery end-diastolic pressure. Finally, in the case of congenitally 'floppy' mitral valves with a mid-systolic click, the click may occur sufficiently early in systole to be mistaken for an aortic ejection sound. In difficult cases, echophonocardiographic studies are invaluable in clarifying the diagnosis.

Whether an isolated aortic ejection sound can arise from an abnormality of the ascending aorta, the so-called 'root' sound, is questionable. The 'root' sound said to be found in coarctation of the aorta is, in our experience, invariably accompanied by the echo- and phonocardiographic signs of a bicuspid aortic valve, an association that is well recognised and has been said to occur in up to 75 per cent of cases of coarctation (Smith and Matthews, 1955). So far, our clinical impression of a root sound has nearly always been shown by echophonocardiographic studies to be fallacious, the suspect sound usually coinciding with late tricuspid valve closure. The only exceptions are with the enormous aorta of severe Fallot's tetralogy or pulmonary atresia and it is even possible that the ejection sounds in these patients may result from aortic valve abnormalities (Glancy *et al.*, 1968). Thus, while not denying the possibility that such sounds may result from a greatly dilated aortic root, we share the scepticism expressed by Hancock (1961) concerning their existence.

In conclusion, we believe that the finding of an aortic ejection sound, in the absence of other signs of aortic stenosis, indicates a non-stenotic, bicuspid aortic valve. To be certain of the origin of the sound, it is necessary to record it simultaneously with echocardiograms from all 4 valves to show unique coincidence between the point of halting of the opening aortic valve cusps and the onset of the vibrations of the sound. There are several echo characteristics usually seen with bicuspid

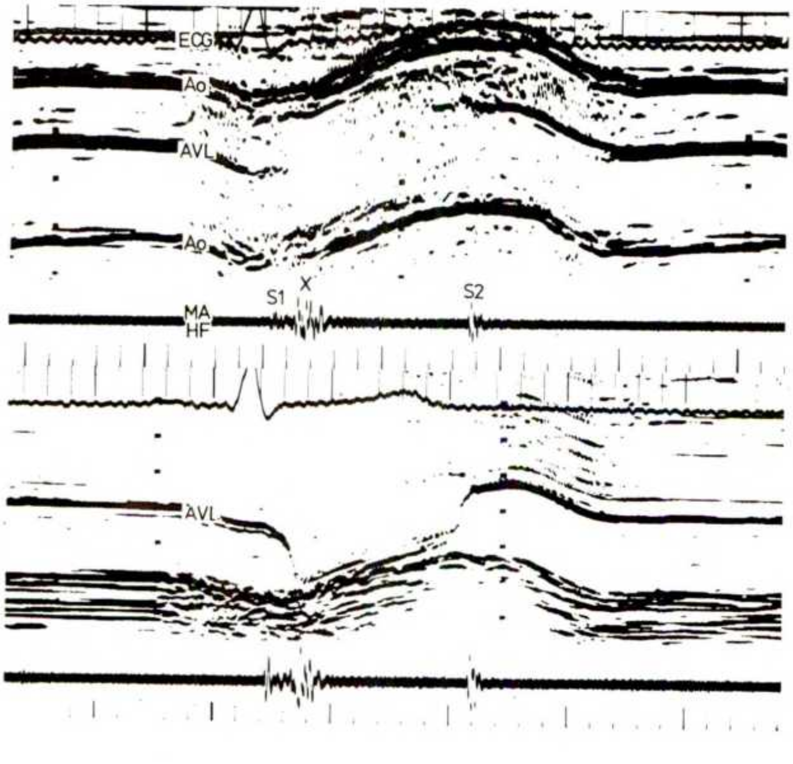

Fig. 7 *Aortic valve echoes from one of the group 3 patients. Despite every effort, the cusps could not be visualised in the conventional view* (top), *so timing of the ejection sound could not be confirmed. However, in the apical view* (bottom), *the onset of the sound is seen to coincide with maximal valve opening and echoes are recorded during systole.*

valves which lend support to the diagnosis. Of particular value are the records obtained by recording the aortic valve from the apex (Fig. 7). This allows both verification of the ejection sound timing and detection of echoes from the valve during systole.

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The natural history of a non-stenotic bicuspid aortic valve[1]

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SUMMARY Forty-one patients in whom the diagnosis of a non-stenotic bicuspid aortic valve had been established by noninvasive techniques were followed up for a mean of 10·9 years. During this period, 2 patients required aortic valve replacement because of the development of calcific aortic valve stenosis at the ages of 52 and 64 and 5 others developed evidence of mild aortic valve stenosis. The appearance of calcium in a bicuspid aortic valve suggests the possibility of subsequent calcific aortic stenosis, and patients with this feature should be carefully followed up.

Bacterial endocarditis on the aortic valve occurred in 3 patients, one of whom developed severe aortic regurgitation and subsequently died. Patients with a bicuspid aortic valve are at definite risk from bacterial endocarditis and should receive appropriate antibiotic prophylaxis. In 26/41 (63%) patients there was no clinical change during the follow-up period, including 7 of the patients over the age of 50.

Over 400 years ago, Leonardo da Vinci sketched aortic valves with 2, 3, and 4 cusps. He concluded that the optimal relation between structure and function would be provided by a valve with 3 cusps. Osler (1886), however, found that a bicuspid aortic valve may be encountered as an incidental finding at necropsy and the fact that such a valve may still be functioning normally in the seventh and eighth decades of life has been subsequently confirmed (Wauchope, 1928; Edwards, 1961; Roberts, 1970; Pomerance and Davies, 1975; Fenoglio *et al.*, 1977). On the other hand, a bicuspid aortic valve may be the site of infective endocarditis or calcific aortic stenosis. Osler's interest in bicuspid aortic valves was stimulated by his finding of bacterial endocarditis on such a valve and the importance of this was emphasised by Lewis and Grant (1923). Calcific aortic stenosis occurring in a bicuspid aortic valve was first recognised by Peacock in 1868, but despite this observation, it was generally thought that isolated calcific aortic stenosis occurring in adults was the result of rheumatic valvular disease (Karsner and Koletsky, 1947). Because of the frequent history in these patients of a murmur since infancy, Campbell and Kauntze (1953) suggested that there might be an underlying congenital abnormality and in 1959 Bacon and Matthews showed that in many cases of isolated calcific aortic stenosis, the aortic valve was bicuspid.

Although a bicuspid aortic valve is the commonest congenital anomaly of the heart (Wauchope, 1928), the incidence of the complications of infection and stenosis will remain unknown until the presence of the abnormality can be detected during life (Bacon and Matthews, 1959). Evidence has now accumulated to indicate that an isolated aortic ejection sound, identified by its relation to aortic valve movement, and confirmed by the echocardiographic appearance of the valve, is an accurate indication of the presence of a non-stenotic bicuspid aortic valve (Leech *et al.*, 1978). Since 1950, otherwise normal subjects thought to have an isolated aortic ejection sound have been indexed and this study presents the results of follow-up of these patients, the survivors being re-examined by one of us and investigated by echophonocardiography.

Patients and methods

PATIENTS

Since 1950, 54 subjects with an early systolic sound, thought to be an aortic ejection sound, documented by phonocardiography and carotid pulse tracings, have been indexed and form the basis of the present study, None of the patients had evidence of aortic stenosis or regurgitation when first seen. The original electrocardiogram and chest *x*-ray film were normal apart from slight prominence of the ascending aorta in some cases

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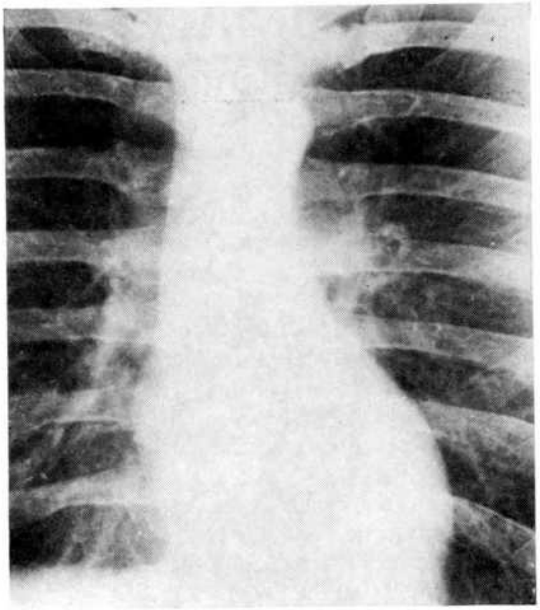

Fig. 1 *Chest* x-*ray of case 24 who has no signs of deterioration after 14 years follow-up, showing slight prominence of the border of the ascending aorta, typical of a non-stenotic bicuspid aortic valve.*

(Fig. 1). A minimal follow-up period of 5 years was required for inclusion in the study.

DEFINITION OF STUDY GROUP

Review of the original phonocardiograms showed that in 6, either the carotid upstroke or the left ventricular ejection time marginally exceeded normal limits (Bonner *et al.*, 1973). This suggested that a minimal degree of stenosis may have been present, though the systolic murmur was soft enough to have been physiological, the carotid pulse felt normal, and there was no clinical or electrocardiographic evidence of left ventricular hypertrophy. In a further 7 patients, the echophonocardiogram disclosed that the original diagnosis of an aortic ejection sound was incorrect and this was usually caused by confusion with a loud late tricuspid component of the first heart sound. These 13 patients were, therefore, excluded from further consideration, leaving 41 patients in the study group.

When first seen their ages had ranged from 1 week to 64 years and, excluding the deaths, the age range at follow-up was 6 to 71 years. Twenty-eight were male and 13 female, giving the same preponderance of males as is found in isolated aortic stenosis. Seven had previously had a coarctation of the aorta resected.

The evidence for the diagnosis of a bicuspid aortic valve in these 41 patients was as follows:

(A) A bicuspid aortic valve was found at operation or necropsy in 7 patients.

(B) In 27 patients echophonocardiographic studies showed coincidence of the moment of halting of the opening aortic valve cusps and the onset of the vibrations of the ejection sound on the phonocardiogram. In every case the echocardiographic features of a bicuspid aortic valve were also seen. These consisted of either an eccentricity index greater than 1·25 (Nanda *et al.*, 1974; Radford *et al.*, 1976) or, in the apical view, the presence of echoes from the aortic cusps throughout systole (Leec *et al.*, 1978).

(C) In 3 cases, the technical quality of the echo recordings was poor, and in 4 more, echo studies were not performed. In these 7 patients, the diagnosis of a bicuspid aortic valve rests on the finding of an aortic ejection sound identified by a phonocardiogram with a simultaneous carotid pulse recording.

METHODS

The investigations carried out on the patients in this study were as follows:

(1) Careful review of the clinical history, the relation of the ejection sound on the original phonocardiograms to the carotid pulse tracing, and the original electrocardiogram and chest *x*-ray film (Fig. 1).

(2) A clinical examination, electrocardiogram and chest *x*-ray were performed on all the living patients. In patients in whom the echocardiogram or the lateral chest *x*-ray film suggested that there might be calcium in the aortic valve, *x*-ray screening with image amplification was carried out to determine the presence or quantity of calcification.

(3) A standard echocardiographic study.

(4) In order to determine whether or not the 'ejection sound' originated from the aortic valve simultaneous phonocardiogram and echocardiograms were recorded at 200 mm/s (Leech *et al.*, 1978). Particular attention was paid to the moments of aortic valve opening and tricuspid valve closure.

(5) External carotid pulse tracings were recorded and the 'T-time', or time to half maximal upstroke excursion (Epstein and Coulshed, 1964) and the left ventricular ejection time (Weissler *et al.*, 1968) were measured.

Results

The findings in 41 patients are summarised in Table 1. The minimal duration of follow-up was 5 years the longest being 25 years, the mean 10·9 years and the median 11 years.

Table 1 *Results of follow-up of 41 patients initially presenting with signs of a non-stenotic bicuspid aortic valve: minimum follow-up period was 5 years, with the exception of 2 patients in whom the diagnosis was confirmed at necropsy*

Case no.	*Age at final examination (y)*	*Age first seen*	*Sex*	*Years followed up*	*Developments during follow-up period*			
					Stenosis	*Calcium*	*BE*	*Regurgitation*
1	6	1/52	M	6				
2	9	4	M	5				
3	14	5	F	9				
4	15	5	M	10				
5	15	8	F	7	+			
6	15	4	F	11				
7	15	5	M	10				
8	15	8	M	7				
9	16	4	M	12				
10	16	5	F	11				
11	16	6	M	10				
12	16	1	F	15	+			
13	18	12	F	6				
14	18	6	F	12				
15	20	13	F	7				
16	29*	24	F	5			+	
17	22	15	F	7				
18	22	6	M	16				
19	23	7	F	16				
20	25	18	F	7				
21	29	14	M	15				+
22	32	19	F	13				
23	37	29	M	8				
24	37	23	M	14				
25	37	28	M	9			+	++
26	39*	28	F	11			+	+++
27	39	30	M	9				
28	45	34	M	11				+
29	46	38	F	8	+	+		+
30	47	36	M	11				
31	50*	49	M	3/12				
32	52	41	M	11	+	+		
33	53	28	M	25				
34	55†	40	M	15	+++	+++		
35	54	37	M	17				
36	57*	46	M	11				
37	60*	57	M	3		+		
38	62	50	M	12				
39	63	47	M	16				
40	64†	49	M	15	+++	+++		
41	71	64	M	7	+	+		+

*Death.
†Valve replacement for severe stenosis.
+, slight; ++, moderate; +++ severe.
BE, bacterial endocarditis.

Table 2 *Details of 5 patients who died during follow-up, in 4 of whom the diagnosis of bicuspid aortic valve was confirmed at necropsy*

Case no.	*Age*	*Cause of death*	*State of aortic valve*
26	39	Bacterial endocarditis	Bicuspid, non-stenotic bacterial endocarditis
16	29	Drug overdose	Unknown
31	50	Myocardial infarction	Bicuspid, non-stenotic
36	57	CVA	Bicuspid, non-stenotic
37	60	Ischaemic heart disease	Bicuspid, non-stenotic minimal calcification

CVA, cerebrovascular accident.

1. DEATHS

Five patients died during the follow-up period (Table 2). In 3 patients (cases 31, 36, and 37) the clinical diagnosis of a bicuspid aortic valve was confirmed at necropsy, the cause of death being unrelated to the valve abnormality. In no case was there significant obstruction to left ventricular outflow. Though case 37 had slight calcification of the aortic cusps, cardiac catheterisation 3 years before death had shown no gradient across the valve. Case 22 had had bacterial endocarditis with trivial aortic regurgitation, but post-mortem information about the valve was not available; death was the result of a drug overdose.

The fifth patient (case 26) who died aged 39 having been followed clinically for 11 years, was the only one in whom the cause of death was related to a bicuspid aortic valve. When she was first seen, a diagnosis of *Streptococcus viridans* endocarditis was made and an isolated aortic ejection sound was recorded. She was successfully treated with penicillin and subsequently noted to have trivial

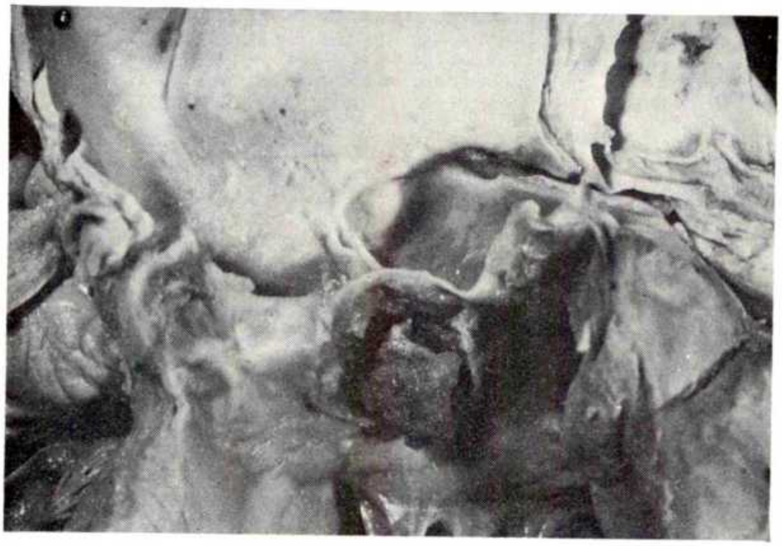

Fig. 2 *Aortic valve of case 26 whose death was related to bacterial endocarditis on a bicuspid aortic valve. The single commissure can be seen, with a large vegetation beneath the cusps, embolisation from which was probably the cause of death.*

aortic regurgitation. Despite penicillin prophylaxis, she suffered a second attack of *Streptococcus viridans* endocarditis 4 years later. Treatment with penicillin was again successful, but she was left with clinical signs of severe aortic regurgitation, declined further investigation and treatment, and died suddenly, probably from a cerebral embolus. A large friable calcified vegetation was found on the aortic valve (Fig. 2), but unfortunately examination of the brain was refused.

(2) BACTERIAL ENDOCARDITIS

Three of the patients developed bacterial endocarditis on the aortic valve during the follow-up period, the infecting organism in each case being *Streptococcus viridans*. None had gross dental sepsis or had undergone any recent dental procedure. Two of them had a second episode of infection, again unrelated to a dental procedure. As a result, one patient was left with severe aortic regurgitation and subsequently died, as described above. Of the other 2 patients, one has moderately severe aortic regurgitation and the other patient only slight regurgitation.

(3) SEVERE AORTIC STENOSIS

Two of the male patients developed aortic stenosis necessitating valve replacement. The first was 40 years old when first seen, and had an aortic ejection sound with a soft systolic murmur, normal carotid pulse, and normal electrocardiogram. Twelve years later, the ejection sound had disappeared, and he had developed a loud systolic murmur (Fig. 3). The *x*-ray film showed gross calcification of the aortic valve and the electrocardiogram showed left ventricular hypertrophy; there was a pressure gradient of 70 mmHg (9·3 kPa) across the valve. At operation aged 52 a calcified bicuspid aortic valve was found and was successfully replaced.

The second patient was 49 when first seen in 1960. The aortic ejection sound was accompanied by a soft ejection systolic murmur, but the electrocardiogram was normal and no valve calcification was apparent on the *x*-ray film. By 1974, there was clinical evidence of severe aortic stenosis, the ejection sound had disappeared, and a peak pressure gradient of 100 mmHg (13·3 kPa), was measured across the valve. At operation, when the patient was 64, the valve was found to be heavily calcified and bicuspid (Fig. 4), and was replaced.

(4) (a) MILD AORTIC STENOSIS

Four patients have developed mild aortic stenosis over a period of 7 to 15 years. Though the electrocardiogram remains normal there has been an increase in the intensity of the murmur, slowing of the carotid pulse upstroke, and lengthening of left ventricular ejection time and T-time. In the 2 patients over 30, these changes have been accompanied by radiological and echocardiographic evidence of valve calcification. In the 2 under 30, there is no evidence of calcification (Table 3).

(4) (b) MILD AORTIC REGURGITATION

The appearance of an early diastolic murmur at the left sternal edge indicates the development of slight aortic regurgitation in 3 patients in whom there has been no evidence of bacterial endocarditis. One of these patients (case 29) also has mild stenosis. Another required mitral valve replacement for

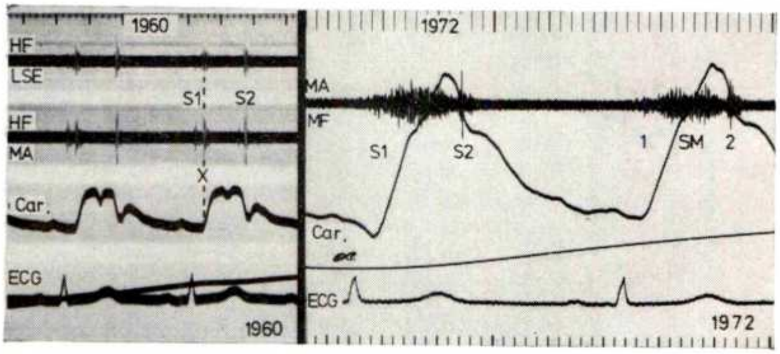

Fig. 3 *Phonocardiograms of case 34. On the left is the recording made in 1960 showing the aortic ejection sound (x), with no systolic murmur and a normal carotid pulse. By 1972 the ejection sound had disappeared, a loud ejection systolic murmur was present, and the carotid upstroke was slow. At operation the valve was shown to be heavily calcified and bicuspid.*

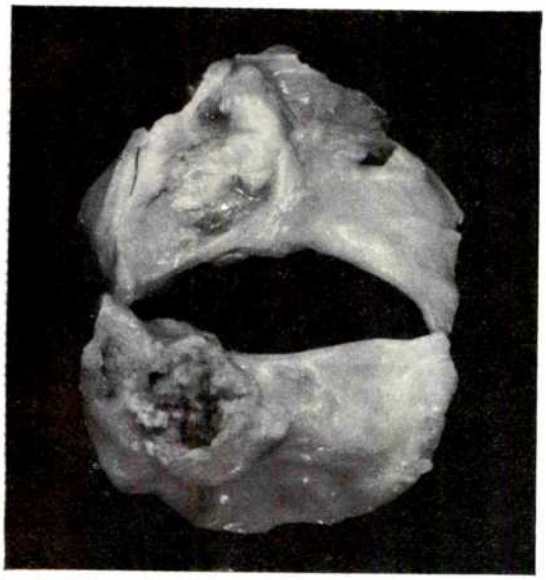

Fig. 4 *The aortic valve of case 40, replaced at age 64, When first seen, he had an isolated aortic ejection sound. Fifteen years later, he had signs of severe aortic stenosis and the peak pressure gradient across the valve was 100 mmHg (13·3 kPa). The valve is heavily calcified and bicuspid.*

Table 3 *Development of aortic stenosis and valve calcification in relation to age of the patient*

Condition of aortic valve	*Patients under 30 years (total 21)*	*Patients over 30 years (total 20)*
No stenosis	19	14
Mild stenosis without calcification	2	0
Mild calcification without significant stenosis	0	1
Mild stenosis with calcification	0	3
Aortic valve replacement for severe calcific aortic stenosis	0	2

severe mitral regurgitation caused by bacterial endocarditis on a floppy mitral valve. At operation the aortic valve was found to be bicuspid and because of the slight regurgitation was replaced (Fig. 5).

(5) NO CLINICAL CHANGE

In the remaining 26 patients, the original clinical finding of an aortic ejection sound without any other signs of aortic stenosis has not changed (Fig. 5 Seventeen are less than 30 years of age and their mean follow-up is 10·0 years. The mean follow-up of the 9 patients who are over 30 is 13·9 years.

Discussion

As a result of an interest in ejection sounds (Leatham and Vogelpoel, 1954) and the observation that they occasionally occur in 'normal' children (Leatham *et al.*, 1963), it was speculated that an isolated aortic ejection sound might indicate the presence of a non-stenotic bicuspid aortic valve. Patients in whom an isolated aortic ejection sound had been recorded phonocardiographically were, therefore, followed up, and the survivors were investigated using echophonocardiography. Using the criteria which have been developed for the non-invasive diagnosis of a bicuspid aortic valve (Leech *et al.*, 1978), confirmation of the original clinical diagnosis was obtained in 41 patients. In every instance where direct examination of the valve at necropsy (4 cases) or surgery (3 cases) has been possible, the diagnosis of a bicuspid aortic valve has been confirmed.

We are thus able to report a follow-up of from 5 to 25 years (mean 10·9 years) in a group of 41 subjects with evidence of an uncomplicated bicuspid aortic valve at the first examination (Table 1). One has died as a result of bacterial endocarditis; 2 have developed calcific aortic stenosis requiring valve replacement; 3 have had bacterial endocarditis which led to significant aortic regurgitation in 2. There are 4 instances of the development of mild

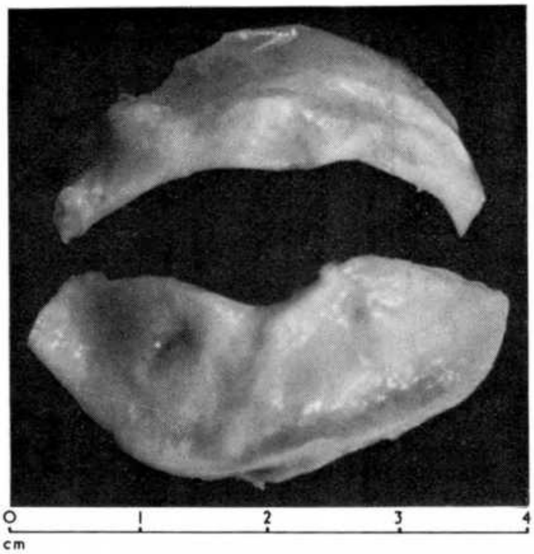

Fig. 5 *The aortic valve removed surgically from case 41 at age 71. There is minimal calcification in the bases of the cusps. Peak gradient at catheterisation was 12 mmHg (1·5 kPa).*

aortic stenosis and 3 of slight regurgitation unrelated to infection. In 26 subjects, the signs of an uncomplicated bicuspid aortic valve have not altered, and they remain asymptomatic. One of these is now 53 years old and has been followed for 25 years.

The 2 patients requiring valve replacement developed severe calcific aortic stenosis at the ages of 54 and 64 years, indicating that calcification, severity of aortic stenosis, and increasing age are closely interrelated. The severity of the stenosis appears to have progressed relatively rapidly once calcium appeared. Paget (1844) suggested that bicuspid aortic or pulmonary valves 'are very liable to disease'. Because of their configuration, the free edges of the cusps of such valves are subjected to increased stress during systole (Edwards, 1961), and this may account for the tendency for a bicuspid aortic valve to calcify. Smith and Matthews (1955) suggested that with coarctation of the aorta the added stress of systemic hypertension may have led to the high incidence of calcific aortic stenosis on bicuspid aortic valves in these patients. However, as pathological studies have emphasised (Wauchope, 1928; Roberts, 1970; Fenoglio *et al.*, 1977), not all bicuspid aortic valves become calcified, and there were 9 patients in our series over the age of 40 in whom there were no signs of calcification or stenosis.

In view of the frequent finding of coronary atheroma in patients with aortic stenosis, it has been suggested (Bacon and Matthews, 1959) that the atheromatous state causing the coronary disease is also responsible for aortic cusp stiffening. The results of the present study do not provide evidence to support this concept. Two of our patients died of coronary disease; one had, in addition, widespread severe atheroma of his iliac and femoral vessels requiring surgical treatment, but only minimal deposition of calcium in the aortic valve cusps; the other had a normally functioning bicuspid valve. Moreover, atherosclerosis is a disorder of the endothelium and intima of the arterial wall, whereas calcification and stiffening of a bicuspid valve starts in the cusp fibrosa, as it does in a tricuspid aortic valve at a greater age (aortic sclerosis). Thus our findings are more suggestive of a premature ageing process as the cause of calcification and stenosis on a congenitally abnormal valve, rather than this being the result of an atheromatous diathesis.

Calcification on a bicuspid aortic valve is rare before the age of 30 (Campbell, 1968). In our series only 2 patients developed stenosis before this age, and in both cases the degree of stenosis was mild and was not associated with calcium (Table 3). This contrasts with the natural history of patients who have a congenitally stenotic valve when they are first seen, since haemodynamic studies (Cohen *et al.*, 1972; El Said *et al.*, 1972) have shown that

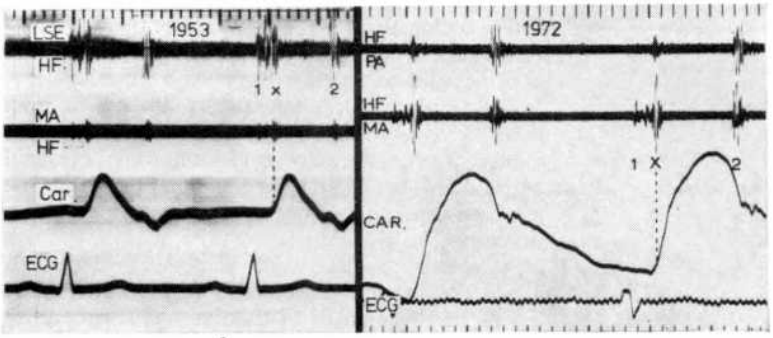

Fig. 6 *Phonocardiograms of case 33 taken in 1953 and 1972. The only abnormality is the lone aortic ejection sound which remains unchanged over a follow-up period of 25 years.*

in many of these patients the severity of the stenosis tends to increase. With the exception of those patients who developed bacterial endocarditis, aortic regurgitation was not an important complication, occurring to a mild degree in only 3 cases. Significant aortic regurgitation may present with a bicuspid valve but it is likely that the regurgitation is long standing, and therefore such patients would not have been included in our study group.

The present study confirms the susceptibility of a bicuspid aortic valve to bacterial endocarditis which occurred in 3 patients. Two patients suffered a second episode. Endocarditis was responsible for the only valve-related death in our series. The finding of an isolated aortic ejection sound is, therefore, an indication for antibiotic prophylaxis before dental treatment or other procedures likely to produce bacteraemia. It may even be significant in planning contraception in view of the report by De Swiet *et al.* (1975) of endocarditis on a bicuspid aortic valve after insertion of an intrauterine contraceptive device.

It is reassuring to find no detectable change in 26 of the 41 patients (63%), followed up for a mean of 11·3 years, including 7 out of the 10 patients over the age of 50.

Deterioration caused by the development of calcific aortic stenosis is most unlikely before the age of 40 and so, apart from the risk of bacterial endocarditis against which precautions can be taken, a young person found to have an isolated aortic ejection sound can be assured of a good prognosis for at least 25 years. At present we see older patients every 3 years, increasing the frequency of follow-up if calcification of the aortic valve is detected.

Continued follow-up of the patients reported here will be required before the precise incidence of severe aortic stenosis on a previously non-stenotic bicuspid aortic valve can be determined.

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Effect of aortic valvular regurgitation upon the impedance cardiogram[1]

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SUMMARY The first derivative thoracic impedance cardiogram, phonocardiogram, and electrocardiogram were recorded in three groups of 22 subjects each. In Group 1 (control), simultaneous impedance cardiogram, phonocardiogram, and aortic valve echocardiograms showed that the X point of the impedance cardiogram occurred synchronously with the aortic second heart sound and with echocardiographic aortic valve closure. In group 2 (clinical diagnosis of aortic regurgitation) the scalar magnitude of the impedance cardiogram O wave and the ratios of the impedance cardiogram wave form $X/dz/dt_{max}$ and $O/dz/dt_{max}$ were different from control. In addition, the early diastolic ($\overline{X}$) and systolic portions ($\overline{S}$) of the impedance cardiogram wave form of group 3 patients were planimetered and expressed as the ratio $\overline{X}/\overline{S}$, called the impedance cardiographic aortic regurgitant fraction (aortic RF_I). The aortic RF_I was increased by handgrip, a manoeuvre which acutely increases the magnitude of aortic regurgitation. The difference between Fick cardiac output and left ventricular angiographic output was used to calculate aortic valvular regurgitant fraction, which related closely to the impedance cardiogram. These data suggest that it is useful in the noninvasive assessment of aortic regurgitation.

The impedance cardiogram was developed by Kubicek *et al.* (1966) as a noninvasive system to monitor cardiac output. This instrument applies a constant current across the chest and the impedance to the current is recorded. Typical records of the impedance cardiogram are shown in Fig. 1 and 2.

A previous study from our laboratory, which recorded the impedance cardiogram and the phonocardiogram simultaneously, showed that the impedance cardiogram X point occurs synchronously with the aortic component of the second heart sound (Lababidi *et al.*, 1970). We have observed the X point to be deeper in subjects with aortic regurgitation than in normal subjects. A study previously reported from our laboratory indicated that though the impedance cardiogram could estimate cardiac output in children, in patients with aortic regurgitation, the impedance cardiogram overestimated the Fick cardiac output (Lababidi *et al.*, 1971). These observations suggested that the impedance cardiogram was affected both in contour and magnitude by aortic regurgitation and might reflect the total left ventricular systolic output, including the regurgitant fraction.

The impedance cardiogram ratio $X/dz/dt_{max}$ appears to correlate with the severity of aortic regurgitation (Schieken *et al.*, 1975). To confirm these observations, we induced experimental aortic regurgitation in dogs using a specially designed catheter. The aortic regurgitant fraction was calculated using an electromagnetic flowmeter integrated forward and reverse aortic flows. These animal data suggested that the ratio of the area under the X wave divided by the area under the dz/dt_{max} herein called the impedance cardiogram aortic regurgitant fraction (aortic RF_I) correlated well with the regurgitant fraction ($r = 0{\cdot}87$) computed from the flowmeter measurements in these animals (Patel *et al.*, 1976).

With these observations in mind, we planned this clinical study to investigate further the temporal relation of the X point to echocardiographic aortic closure and to determine the correlation of the impedance cardiogram aortic RF_I to the aortic

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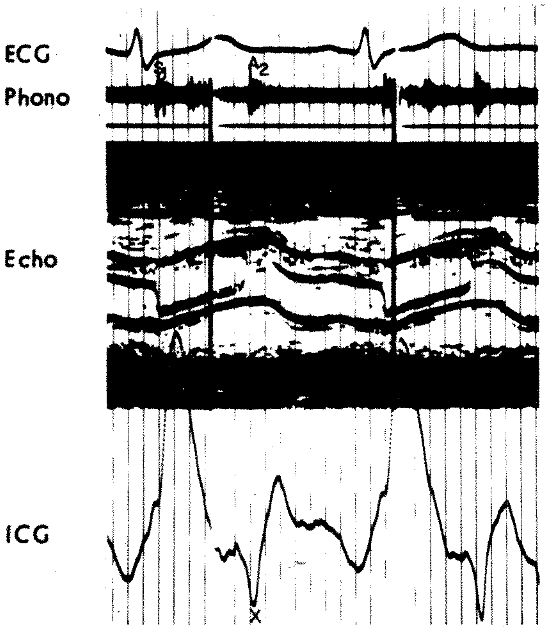


Fig. 1 *Simultaneous recording of the electrocardiogram (ECG), phonocardiogram (phono), echocardiographic aortic valve tracing (echo), and the impedance cardiogram (ICG) in a 10-year-old boy (group 1) with a clinical diagnosis of innocent pulmonary flow murmur. The echocardiographic aortic valve closure occurs shortly before the aortic component of the second heart sound (A_2), but synchronously with the nadir of the ICG X point (x).*

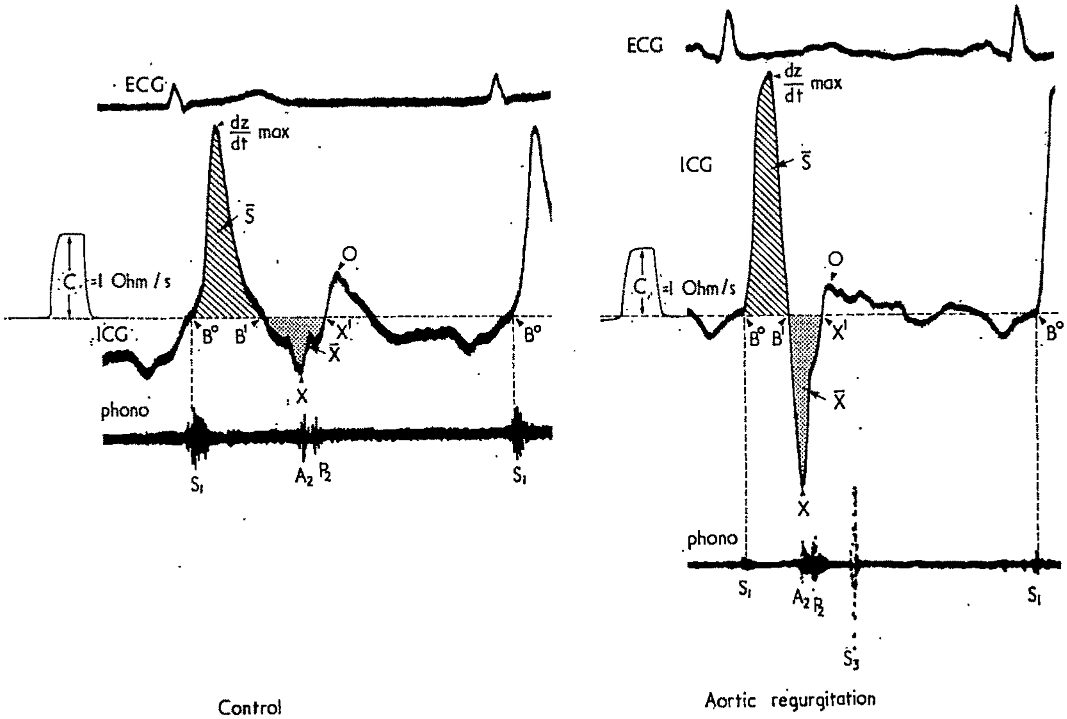
regurgitant fraction calculated in patients undergoing cardiac catheterisation.

Subjects and methods

The impedance cardiograms of 22 control subjects (group 1) with a normal cardiac examination, 22 patients with a clinical diagnosis of mild to moderate aortic regurgitation (group 2), and 22 patients with a cardiac catheterisation diagnosis of aortic regurgitation (group 3) were recorded on a Minnesota impedance cardiogram Model 202 simultaneously with a phonocardiogram and electrocardiogram. The mean age of group 1 was 22·8 years (range 5 to 52), that of group 2 was 23·8 years (range 5 to 71), and that of group 3 was 31·4 years (range 18 to 56). In group 2 patients, the diagnosis of aortic regurgitation was established clinically by the typical auscultatory findings of an early diastolic decrescendo murmur, loudest at the left sternal border. Of 22 group 2 patients, 8 had both abnormal electrocardiograms with left ventricular hypertrophy, T wave changes, and chest *x*-ray films showing increased heart size. The impedance cardiogram was recorded in the following manner. Four coated aluminium Mylar strips with an adhesive tape backing were placed around each subject; two strips were placed around the neck and two around the lower thorax (Lababidi *et al.*, 1971). The upper electrodes on the thorax were placed at the level of the xiphoid process. The electrodes on the neck and trunk were placed at least 3 cm apart. The outer two electrodes were attached to a constant current oscillator supplying alternating current at 100 KHz. The first derivative of the electrical impedance between the inner two electrodes was continuously recorded. Echocardiograms of the aortic valve were recorded using a Smith Kline Ekoline 20 ultrasonoscope with a 2·2 or 3·5 mHz transducer with a 1 μs transmission time and a repetition rate of 1000/s. Simultaneous phonocardiograms, with a frequency filter set from 50 to 100 Hz, were recorded from the second right intercostal space.

The wave form of the impedance cardiogram was recorded simultaneously with the echocardiogram, phonocardiogram, and standard lead II of the electrocardiogram on an Electronics for Medicine DR12 modified for echocardiographic recording in 10 subjects from group 1. The intervals from the Q wave of the electrocardiogram to the X point of the impedance cardiogram and the Q wave to the echocardiographic closure of the aortic valve were measured. The uniformity and accuracy of the paper speed (100 mm/s) were measured from 0·04 s time lines generated within the recorder. All impedance cardiographic tracings were recorded in held midexpiration to minimise respiratory variation. The maximal deflection of dz/dt_{max}, O point, and depth of the X point were measured in ohm/s (Fig. 2). Two ratios dz/dt_{max} and $O/dz/dt_{max}$ were calculated.

Group 3 patients with aortic valvular regurgitation underwent cardiac catheterisation. Oxygen consumption was measured using a Wright respirometer and a Beckman E_2 oxygen analyser. The expired air volumes were measured for 3 minutes. Cardiac output was measured by the Fick method. Left ventricular cineangiograms were performed in the right anterior oblique position. All data were analysed randomly without previous knowledge of patient identification. Ventricular volumes were computed using the formula: volume calculated $(V_c) = \frac{\pi}{6}M^2L(CF)^3$, where M = minor axis in centimetres, perpendicular to a major



Control

Aortic regurgitation

Fig. 2 *The left panel shows the electrocardiogram (ECG), the impedance cardiogram (ICG), and phonocardiogram (phono) of a control subject. Before the ICG, a calibration of 1 ohm/s is recorded. The maximum upward deflection occurs during systole (dz/dt_{max}). The nadir of the X wave, the X point, occurs with the aortic component of the second heart sound. The smaller positive deflection, the O wave, occurs during rapid diastolic filling. The right panel shows a similar recording in a patient with an aortic regurgitant fraction of 48 per cent. The striped area ($\bar{S}$) defines the area under dz/dt_{max} or the systolic portion of the ICG. The stippled area $\bar{X}$ is the early diastolic portion. The area boundaries are (B° to B′ and B′ to X′) the intersections of these wave forms with a line drawn through the B° of two successive ICG wave forms. The area $\bar{X}$ divided by the area $\bar{S}$ is called the impedance cardiogram aortic regurgitant fraction (aortic RF_I).*

axis at mid point, L = major axis in centimetres, taken from the left atrioventricular intersection to apex, and CF = correction factor (Greene *et al.*, 1967). This volume was further corrected using the formula (Kennedy *et al.*, 1970): volume = $V_c \times 0{\cdot}81 + 1{\cdot}9$.

The Fick angiographic aortic regurgitant fractions were expressed as the difference between the cineangiographic left ventricular volumes and Fick cardiac output divided by the cineangiographic left ventricular volumes (Kubicek *et al.*, 1966). Impedance cardiograms were performed at cardiac catheterisation during the measurement of oxygen consumption. The planimetered areas $\bar{X}$ and $\bar{S}$ were measured using a Keuffel-Esser hand planimeter (Fig. 2). The baseline was established by drawing a line between the B° of two successive beats. The B° which marks the beginning of isovolumetric contraction was identified by the first high frequency component of the first heart sound (Lababidi *et al.*, 1970). The X wave of the impedance cardiogram was identified and boundaries of that wave which crossed the drawn baseline were B′ and X′ (Fig. 2). The planimetered areas B′ to X′ ($\bar{X}$) and B° to B′ ($\bar{S}$) were used to compute the ratio $\bar{X}/\bar{S}$. This ratio was called the impedance cardiographic aortic regurgitant fraction (aortic RF_I).

For each subject in group 3, a correlation was sought between the impedance cardiogram $\bar{X}$ and the Fick angiographic regurgitant volume. In addition, a correlation was sought between the impedance cardiogram $\bar{S}$ and the cineangiographic left ventricular stroke volume.

Because our data showed a high correlation between $\bar{X}$ and regurgitant volume and a similar high correlation between $\bar{S}$ and left ventricular stroke volume, by substituting $\bar{X}$ and $\bar{S}$ into the standard formula for cardiac catheterisation determined aortic regurgitant fraction (AR_{fx}), we derived aortic RF_I

$$AR_{fx} = \frac{\text{Cineangiographic LVSV} - \text{Fick stroke volume}}{\text{Cineangiographic LVSV}}$$

$$= \frac{\text{Regurgitant stroke volume}}{\text{Cineangiographic LVSV}} \times 100\%$$

Then substituting the impedance cardiogram equivalents of regurgitant volume ($\bar{X}$) and a cineangiographic left ventricular stroke volume ($\bar{S}$) the formula becomes

$$AR_{fx} = \bar{X}/\bar{S}.$$

To test whether indeed the $\bar{X}/\bar{S}$ is a measure of regurgitant fraction it was compared with the catheterisation-measured regurgitant fraction.

After cardiac catheterisation 8 patients of group 3 were asked to perform maximal sustained handgrip, and were then allowed to rest. The impedance cardiogram was measured at rest and during 25 per cent of maximal handgrip during held mid-expiration.

All data are expressed as the mean ±1 standard deviation. The significance of difference between the means was calculated by employing either group or paired t tests.

To test the reliability of the aortic RF_I, we measured an additional 3 beats the next day in 10 patients from group 3. These 3 beats were compared one with another and their average with the previous average aortic RF_I. The reliability between beats within the same individual and between the averages of two different sets of beats was determined for the impedance cardiogram. This was calculated using a 2 factor (randomised block) analysis of variant design.

Results

The X point of the impedance cardiogram is an event that occurs nearly synchronously with aortic valve closure. In 10 of 22 control subjects who had echocardiograms of the aortic valve, the Q to aortic closure time ($0{\cdot}36 \pm 0{\cdot}08$ s) was not significantly different from the Q to X point on the impedance cardiogram ($0{\cdot}34 \pm 0{\cdot}06$) (Fig. 1). An analysis of variance indicated no significant difference between these intervals ($r = 0{\cdot}87$).

The impedance wave for scalar measurements in both group 2 and group 3 were compared with group 1 (Table 1). There was no significant difference between the measurement of the height of dz/dt_{max} or the depth of the X point between the groups. None the less, the X point appeared to be increased in subjects with aortic regurgitation. The O point was diminished ($P < 0{\cdot}01$) in subjects with aortic regurgitation. The ratio $X/dz/dt_{max}$ was increased ($P < 0{\cdot}001$) and the ratio $O/dz/dt_{max}$ was diminished ($P < 0{\cdot}01$) in subjects with aortic regurgitation.

The catheterisation measurements in group 3 patients of left ventricular stroke volume, aortic regurgitant stroke volume, regurgitant fraction, and the impedance measurements, $\bar{S}$, $\bar{X}$, and ratio $\bar{X}/\bar{S}$ are given in Table 2. In group 3 patients (Table 2), there was a range of angiographic stroke volumes of 32 to 156 ml. The impedance area $\bar{S}$ correlated ($r = 0{\cdot}96$) with left ventricular stroke volume; while $\bar{X}$ correlated ($r = 0{\cdot}89$) with aortic regurgitant volume. The ratio $\bar{X}/\bar{S}$, the aortic RF_I, correlated highly with the angiographic aortic regurgitant fraction ($r = 0{\cdot}90$). This relation is shown in Fig. 3.

Sustained handgrip of 25 per cent maximum grip increased the aortic RF_I in all 8 patients. The aortic RF_I rose from a resting level of $0{\cdot}48 \pm 0{\cdot}09$ to $0{\cdot}71 \pm 0{\cdot}1$ ($P < 0{\cdot}01$).

Statistical analysis of the reproducibility of the impedance cardiogram measurements ($\bar{X}$, $\bar{S}$) showed that the intraclass correlation coefficient was 0·94 between beats within the same individual and 0·85 between the averages of two different sets of beats in the same individual recorded on the next day.

Discussion

The data presented confirm the temporal relation of the impedance cardiogram X point to aortic closure. This temporal relation allows the impedance cardiogram X point to be a useful marker

Table 1 *First derivative impedance cardiogram measurements in control subjects and patients with aortic regurgitation*

Subjects	*No.*	*dz/dt*max (Ωs)*	*X point* (Ω/s)*	*O point* (Ω/s)*	*X*	*O*
					*dz/dt*max	*dz/dt*max
Group 1	22	2·64 ±0·95	0·93 ±0·36	0·42 ±0·24	0·35 ±0·02	0·16 ±0·08
Group 2	22	2·50 ±1·08	1·20 ±0·51	0·17 ±0·09†	0·51 ±0·19†	0·08 ±0·07†
Group 3	22	2·73 ±0·96	1·57 ±0·49	0·15 ±0·08†	0·46 ±0·12†	0·08 ±0·08†

*These values are the means and standard deviations of the maximal heights or depths of these points.

†Indicates a significance level of $P < 0{\cdot}01$, comparing group 1 measurements (control) with group 2 or group 3 by group t tests.

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Table 2 *Cardiac catheterisation and impedance cardiogram data in group 3 subjects* ($n = 22$)

$\bar{S}$ *(Ohms)*	*Angiographic left ventricular stroke volume (ml/beat)*	$\bar{X}$ *(Ohms)*	*Fick angiographic regurgitant volume (ml)*	*Fick angiographic regurgitant fraction (%)*	*Aortic* RF_I $\bar{X}/\bar{S}$ *(%)*
3·86	192	1·0	42·24	22	26
3·19	160	0·56	32·0	20·3	18
4·02	200	2·13	92·0	46	52
2·3	120	0·60	36·0	30	26
2·5	130	1·65	81·9	63	66
5·5	231	2·02	103·95	45	37
2·3	120	1·0	40·8	34	43
1·8	90	1·0	48·6	54	55
6·6	260	3·4	114·4	44	51
8·4	265	4·8	129·85	49	57
4·8	230	2·6	138	60	54
5·7	240	3·8	156	65	66
4·1	190	2·7	119·7	63	65
1·73	65	1·2	44·2	68	69
2·95	150	1·35	54	36	45
5·3	220	1·9	77	35	36
2·9	145	1·6	63·8	44	55
3·9	195	2·3	109·2	56	58
1·9	90	1·1	54	60	57
3·1	174	1·78	87	50	57
5·4	210	1·8	94·5	45	33
2·8	140	1·5	64·4	46	53

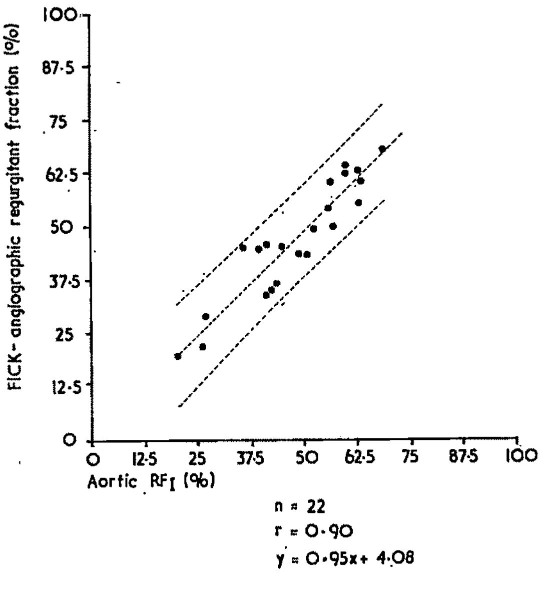

Fig. 3 *Relation of the impedance cardiogram aortic regurgitant fraction (aortic* RF_I*) to the angiographically determined regurgitant fraction. The dotted lines represent the 95 per cent confidence limits.*

for the aortic component of the second heart sound.

The physical principles that govern changes in the impedance cardiogram are not completely understood. Kubicek and others using simultaneous recordings of impedance and aortic flow in dogs showed the relation of peak dz/dt_{max} to the peak aortic ejection rate (Kubicek *et al.*, 1974).

We have shown that the systolic portion of the impedance cardiogram ($\bar{S}$) has a strong correlation with the left ventricular stroke volume as determined by cineangiography. In patients with aortic regurgitation, the cineangiographic left ventricular stroke volume exceeds the Fick calculated cardiac output. The regurgitant volume within the left ventricle is responsible for this discrepancy.

The early diastolic portion of the impedance cardiogram ($\bar{X}$) correlates highly with the per beat volume regurgitated across the aortic valve. This explains the deepened X point observed in subjects with aortic regurgitation. Moreover, the impedance cardiogram ratio $\bar{X}/\bar{S}$, the aortic RF_I, correlates with the resting aortic regurgitant fraction found at cardiac catheterisation.

To test the response of the impedance cardiogram ratio $\bar{X}/\bar{S}$ to acute changes in the regurgitant volume, we employed isometric handgrip exercise, which has been shown to increase the amount of aortic regurgitation (Lind *et al.*, 1964; Kivowitz *et al.*, 1971). Because the aortic RF_I did increase with handgrip, the impedance cardiogram appears to respond concordantly to an acute change in regurgitant volume.

The noninvasive assessment of the severity of aortic regurgitation is difficult. Bounding peripheral pulses are unreliable markers for severe aortic regurgitation (Demany and Zimmerman, 1966). Early mitral valve closure is found by echocardiography with severe aortic regurgitation (Botvinick *et al.*, 1975). Left ventricular dysfunction associated with severe aortic regurgitation correlates with change in fraction of shortening of the echocardiographic minor axis (McDonald, 1976). Moreover, Boughner has found transcutaneous Doppler assessment to relate closely to the regurgitant fraction (Boughner, 1975). Despite these techniques, the clinical assessment of aortic regurgitation remains difficult.

Our findings, both clinical and experimental, suggest that the impedance cardiogram may prove to be a sensitive noninvasive measure of the severity of aortic regurgitation.

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Real-time sector scan study of the mitral valve prolapse syndrome

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SUMMARY Real-time two-dimensional sector scanning was used to analyse mitral valve motion in 4 normal subjects and 6 patients with previously diagnosed mitral valve prolapse syndromes. The normal mitral valve leaflets remain apposed for the duration of systole, and open abruptly with the onset of diastole. During diastole the leaflets are parallel to each other and only the distal ends tend to 'float' closed. Atrial contraction bows the anterior leaflet anteriorly which thus encroaches on the left ventricular outflow tract. The leaflet tips again 'float' closed, but the major portion of the leaflets are not closed until onset of the succeeding left ventricular isovolumic contraction. The abnormal redundant tissue of the ballooning mitral valve is seen as a prominent structure immediately behind the posterior leaflet at the beginning of systole. In one patient with the time-motion pattern of pansystolic prolapse this redundant tissue moved posteriorly in systole and appeared to merge with the left atrial wall. Of the remaining 5 patients, 4 with late systolic prolapse had characteristic movements of this abnormal tissue. With the beginning of systole the redundant tissue moved superiorly and slightly anteriorly into the left atrium. In mid-systole at the time of the diagnostic changes in the standard time-motion study, the abnormal mitral valve tissue moved posteriorly and inferiorly to a position adjacent to the left atrial wall, and then at end-systole moved anteriorly to a mid-atrial position. During diastole the redundant tissue again moved posteriorly, and then again anteriorly to assume its mid-atrial position at the start of the next cardiac cycle. Hence, in at least some patients, the primary abnormality in the mitral valve prolapse syndrome is the mitral valve and not the left ventricle. There is definite prolapse of mitral valve tissue into the left atrium in this syndrome, and the prolapse appears to persist throughout systole regardless of the diagnostic pattern recorded with standard time-motion echocardiography. Furthermore, the redundant mitral valve tissue is the source of several distinct echoes which all follow the outlined course, thus accounting for the multiple parallel systolic echoes often observed in patients with the mitral valve prolapse syndrome.

Since the original description of the mitral valve prolapse syndrome in 1963 (Barlow *et al.*) numerous reports have documented the auscultatory (Barlow, 1965; Kesteloot and Houte, 1965; Barlow and Bosman, 1966; Hancock and Cohn, 1966; Linhart and Taylor, 1966; Behar *et al.*, 1967; Barlow *et al.*, 1968; Bittar and Sosa, 1968; Leachman *et al.*, 1969; Fontana *et al.*, 1970; Jeresaty, 1973), echocardiographic (Shah and Gramiak, 1970; Dillon *et al.*, 1971; Kerber *et al.*, 1971; DeMaria *et al.*, 1974; Cohen, 1976), and angiographic (Dinsmore *et al.*, 1970; Kittredge *et al.*, 1970; Jeresaty, 1971; Gooch, *et al.*, 1972; Liedtke *et al.*, 1973; Scampardonis *et al.*, 1973; Gulotta *et al.*, 1974; Spindola-Franco *et al.*, 1974) features of this distinctive valvular lesion. However, analysis of motion of the mitral valve leaflets in this syndrome has been hampered by technical limitations. Standard one-dimensional time-motion echocardiography can analyse only posterior-anterior movement. Of the usual angiographic projections the left anterior oblique view of the left ventriculogram is thought to be most comparable with the echocardiographic cardiac cross-section (Teichholz *et al.*, 1974). However, superimposition of structures and regurgitant jets of dye into the left atrium often make it difficult to analyse movements of the radiolucent leaflets. As shown by Ranganathan and colleagues (1973) the right

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anterior oblique projection of the left ventriculogram details movement of only the posterior leaflet's three scallops. Furthermore, this radiographic view does not allow accurate analysis of anterior-posterior motion.

Introduction of two-dimensional echocardiographic techniques has expanded our diagnostic ability, and has recently been used to investigate the mitral valve prolapse syndrome. B-scan ultrasonography displays gated, stop-action frames, but has been unable to detect prolapse of mitral leaflets into the left atrium (Millman *et al.*, 1976). However, real-time multiple-crystal (Sahn *et al.*, 1976) and phased array (Gilbert *et al.*, 1976) cross-sectional echocardiographic studies have suggested that during systole mitral leaflets in the prolapse syndrome do arch superiorly into the atrium. The present report details use of a third two-dimensional echocardiographic technique. With the real-time sector scanner it has been possible to show dynamic motion of redundant mitral leaflets during all phases of the cardiac cycle. The scanner clearly depicts systolic prolapse into the left atrium, and suggests that multiple echoes may emanate from a single redundant leaflet.

Methods

All patients studied were referred to the non-invasive laboratory of Montefiore Hospital and Medical Center for diagnostic evaluation. Standard time-motion echocardiographic studies were performed with a Hoffrel Ultrasonoscope, Model 101, and either a 2·25 MHz transducer focused at 7·5 cm or an unfocused 2·0 MHz transducer. The patient was either supine or slightly rotated to the left to enable optimal echocardiographic examination. Echocardiographic information was displayed on a Cambridge multichannel oscillographic recorder and permanent photographic records obtained with a strip chart recorder. A simultaneous electrocardiographic lead II was also continuously recorded.

Six patients with echocardiograms showing the systolic deformity characteristic of the mitral valve prolapse syndrome underwent additional examination with a Hoffrel Mechanical Sector Scanner (also called Wobbler). This scanning echocardiograph uses a standard 2·25 MHz adult cardiac transducer mounted in a special scanning head so it can be oscillated rapidly back and forth over a sector of 35 degrees. The echo signals generated by the scanning system are displayed on a television screen at a rate of 30 frames per second and recorded by a synchronised video tape recorder for later playback and analysis. Selected still frames may be photographed from the television screen during playback with a 35 mm camera. Means are provided in the scanning system to determine accurately the time location of each scanning frame within the cardiac cycle. In the sector scanner used in this study concentric circles of light-emitting diodes provided timing information in tenths and hundredths of a second, with the timing information referenced to a trigger derived from the R wave of the electrocardiogram.

Of the 6 patients studied, 4 were male ranging in age from 14 to 42 years (average 30·8 years). The 2 women were 47 and 51 years old. Two of the male patients and 1 woman had the clinical diagnosis of Marfan's syndrome. One of these was a 14-year-old boy, and the 47-year-old woman with normal body habitus was his mother. One patient had a straight back syndrome without any other apparent cardiac abnormality, and 2 patients had no skeletal or other cardiac lesions.

Standard time-motion and real-time sector scan echocardiograms were done in 4 normal male cardiology residents less than 34-years-old. None had any cardiac symptoms, and all physical examinations were normal.

Results

Routine echocardiographic examinations in the 4 control subjects were normal. A systolic frame from the sector scan of one of these subjects and a line drawing are presented in Fig. 1. The light emitting diodes in the lower left corner indicate that this frame was recorded 0·21 s after inscription of a lead II R wave. The anterior and posterior mitral leaflets are in a closed position, while the proximal aortic root is expanded because of the stroke volume which is being ejected. The left atrium is partially filled. Only the base of the left ventricle is visualised in this frame. Because of the 35° arc it was not possible to record echoes from the mitral valve leaflets and the entire left ventricular silhouette in the same frame. Only portions of the interventricular septum and right ventricular cavity can be defined.

Five selected frames from one cardiac cycle of a sector scan study in a normal subject are shown in Fig. 2. These frames show the movements of the mitral leaflets in diastole and systole. Fig. 3 shows the time motion echocardigram of the same subject, and the arrows mark the approximate times at which the 5 sector scan frames were recorded. At the beginning of systole (0·09 s after R wave inscription) the 2 mitral leaflets are in their closed position, and this position is maintained throughout systole (0·4 s). The systolic leaflet apposition is perhaps better appreciated in the frame recorded at approxi-

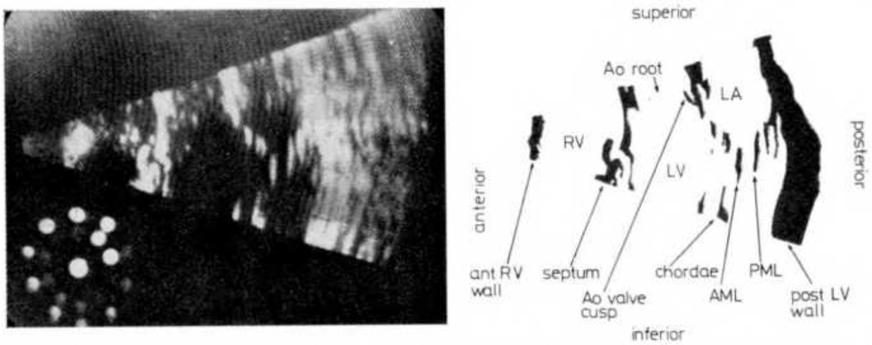
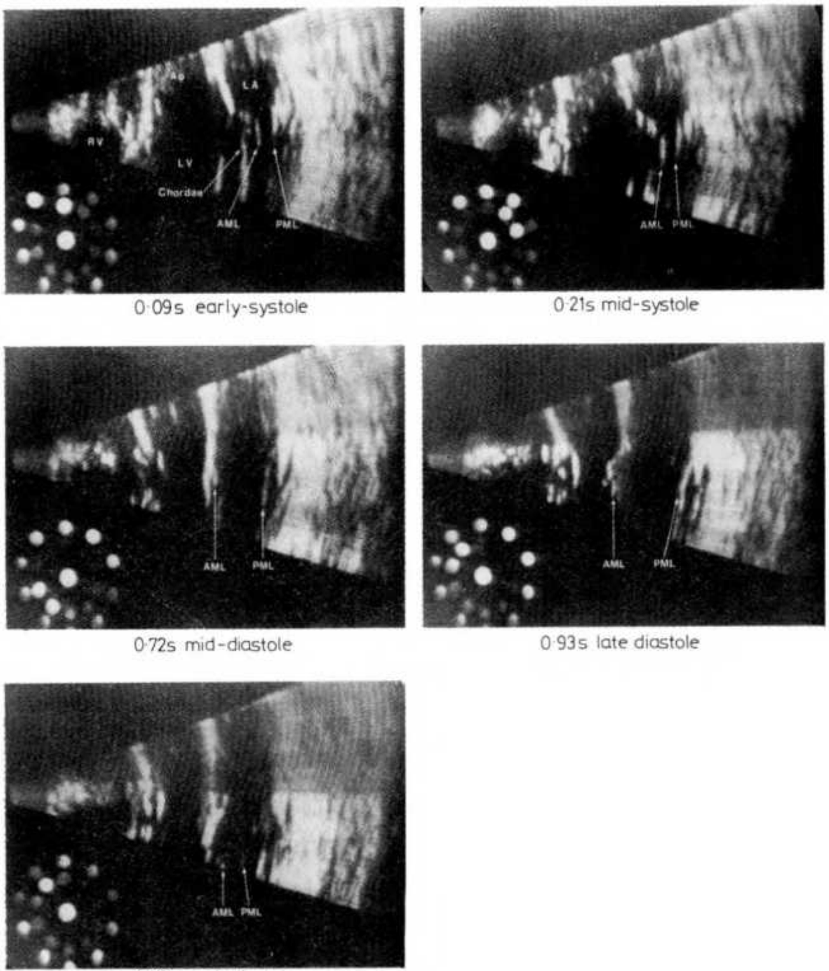


Fig. 1 *Photograph and artist's reproduction of a systolic frame of a real-time sector scan of a normal subject. The anterior (AML) and posterior (PML) mitral leaflets are apposed. The left atrium (LA) and aortic (Ao) root are clearly seen, but only the base of the left (LV) and right (RV) ventricles is visualised because of the boundary imposed by the 35° arc of the mechanically oscillated transducer. Ant, anterior; post, posterior.*



0·09s early-systole

0·21s mid-systole

0·72s mid-diastole

0·93s late diastole

0·98s end-diastole

Fig. 2 *Five sector scan frames from a normal subject showing the motion of the anterior (AML) and posterior (PML) mitral leaflets in systole and diastole. Times refer to the intervals following inscription of the R wave. Abbreviations: see Fig. 1.*

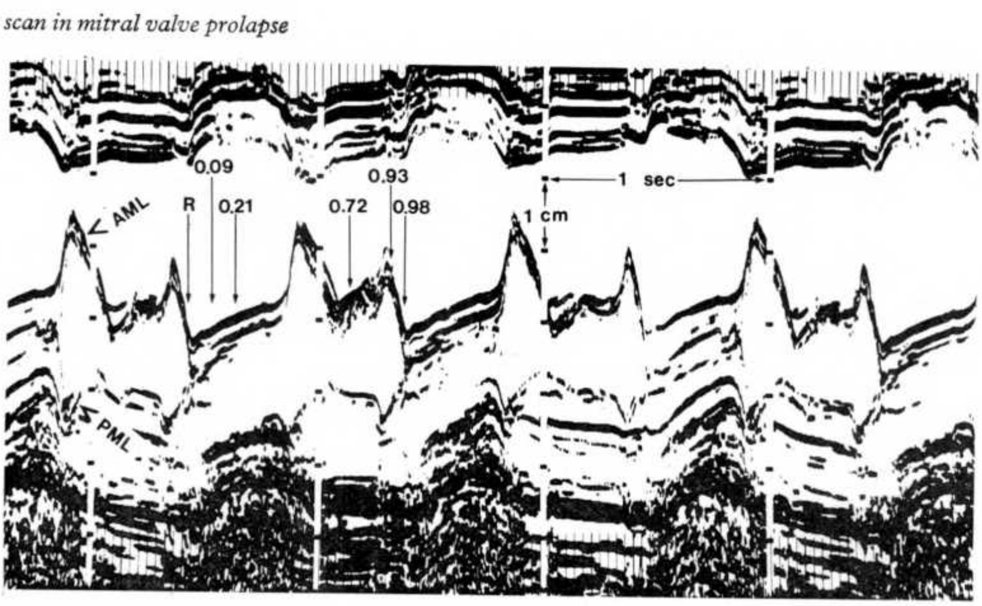
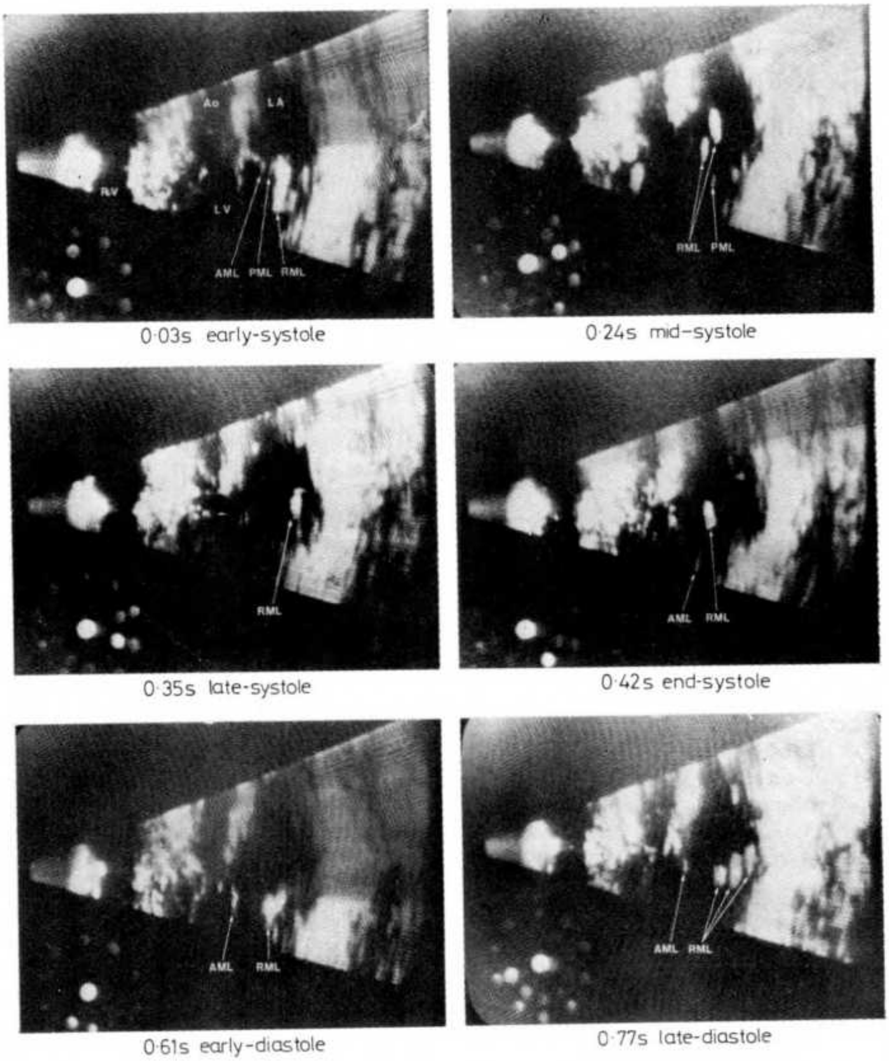


Fig. 3 *Standard time motion echocardiogram of the mitral valve from the same subject whose sector scan is presented in Fig. 2. Arrows mark the intervals (s) after R wave inscription at which the sector scan frames of Fig. 2 were recorded. Abbreviations: see Fig. 1.*

mately 0·21 s after the R wave. At the beginning of diastole the leaflets abruptly open and assume a parallel configuration. Even in mid-diastole (0·72 s) the leaflets are still parallel to each other, and only the most distal parts of the leaflets showed any tendency to float closed. The effect of a vigorously contracting left atrium is seen in the last two frames (0·93 and 0·98 s). In the earlier frame, atrial contraction bows the body of the anterior leaflet anteriorly with consequent encroachment on the left ventricular outflow tract. A comparatively minor posterior movement of the posterior leaflet is also evident. In the last frame only the distal tips of the leaflets are seen to be floating towards each other, while the major distal portions of the leaflets remain parallel. With the start of the new cardiac cycle, isovolumic left ventricular contraction rapidly closes the mitral valve orifice.

Of the 6 patients with mitral valve prolapse syndrome studied by sector scanning, 5 had late systolic prolapse, and 1 had pansystolic prolapse. In the latter patient the prolapsing portion of the valve rapidly moved posteriorly and echoes from the leaflet tissue could not easily be distinguished from those from the left atrial wall. Of the 5 patients with late systolic prolapse, 4 had abnormal sector scans. Six representative frames from the scan of 1 of these patients are shown in Fig. 4, and the corresponding time-motion study is seen in Fig. 5. The first frame recorded 0·03 s after R wave inscription (Fig. 4) shows apposition of the anterior and posterior mitral leaflets. Immediately posterior to the posterior leaflet is a thick, elongated structure which is thought to represent redundant mitral leaflet tissue. In no patient was a similar structure clearly associated with the anterior leaflet. During systole the anterior leaflet is visualised indistinctly, while the posterior leaflet cannot clearly be defined. However, the abnormal mitral valve tissue is clearly visualised, and is mobile. During early systole when the standard echocardiogram shows only minimal anterior excursion of the mitral leaflets, the abnormal leaflet tissue leaves its initial mid-valvular position and moves superiorly and slightly anteriorly. At this time the structure appears to be fragmented. By mid-systole (0·24 s) the redundant mitral tissue has reached its most superior position and now begins to move posteriorly simultaneously with the beginning of posterior sagging of the mitral leaflets seen on the M-mode echocardiogram (Fig. 5); 0·1 s later (0·35 s) when the mitral prolapse is clearly evident on the standard echocardiogram (Fig. 5) the structure has moved inferiorly and posteriorly, and is adjacent to the wall of an expanding left atrium. At end-systole (0·42 s) the abnormal leaflet tissue is again in a mid-valvular position. During early diastole (0·61 s) the apparently fragmented structure again moves posteriorly towards the left atrial wall. Slightly later in diastole (0·77 s) the fragmentation of the abnormal structure is especially



0·03s early-systole 0·24s mid-systole 0·35s late-systole 0·42s end-systole 0·61s early-diastole 0·77s late-diastole

Fig. 4 *Six sector scan frames from a patient with previously diagnosed mitral valve prolapse syndrome. During systole the actual anterior (AML) and posterior (PML) mitral leaflets are not well seen, but the redundant mitral leaflet tissue (RML) can be seen initially to move superiorly and slightly anteriorly into the left atrium, then inferiorly and posteriorly, and finally anteriorly to a mid-valvular position at the end of systole. The abnormal mitral structure at times appears to be fragmented accounting for the multiple systolic echoes recorded on the standard time motion echocardiogram (Fig. 5). Times refer to the intervals after inscription of the R wave. Abbreviations: see Fig. 1.*

distinct. As the left atrial size diminishes there appears to be an anterior movement of the abnormal leaflet tissue.

Abnormal mitral valve structures were identified in 4 patients. The general pattern of superior, slightly anterior, and then inferior-posterior systolic motion was noted in all. In diastole resumption of a mid-valvular position was apparent.

Discussion

Echocardiography is currently used to diagnose a

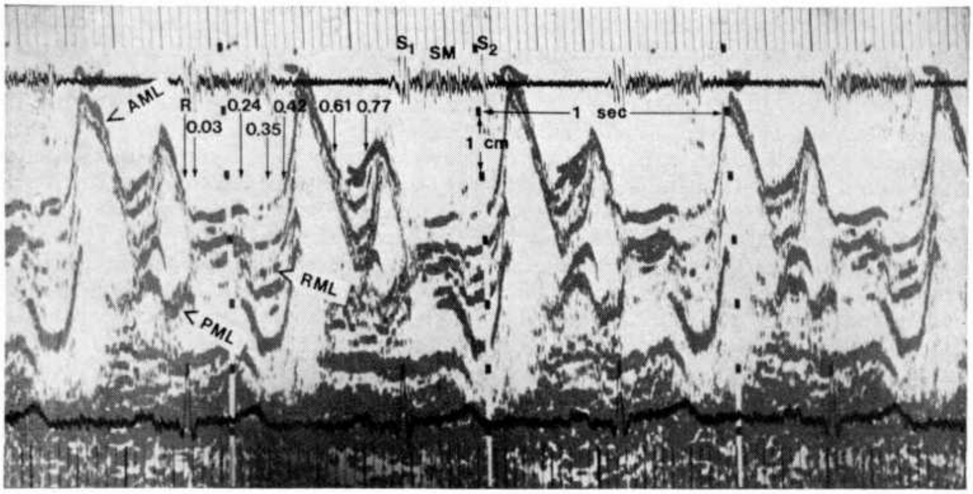


Fig. 5 *Standard time motion echocardiogram of the mitral valve from the same subject whose sector scan is presented in Fig. 4. A mid-systolic prolapse pattern is evident. The multiple parallel systolic echoes probably represent reflection of sound waves from redundant mitral leaflet tissue (RML). Arrows mark the intervals (s) after R wave inscription at which the sector scan frames of Fig. 4 were recorded. Abbreviations: see Fig. 1. SM, systolic murmur.*

variety of adult and paediatric cardiac abnormalities. However, the standard time-motion presentation allows evaluation of structure movement in only an anterior-posterior plane. Furthermore, because movement of only one segment of a structure can be recorded at any given time, the echocardiographer must infer that this motion is representative of the whole. Newer two-dimensional and real-time scanning techniques seek to eliminate these objections. Scans allow evaluation of motion in simultaneous anterior-posterior and superior-inferior planes, and provide echo reception from large contiguous areas.

The sequence presented in Fig. 2 shows the movement of normal mitral leaflets during a cardiac cycle. During the entire systole the leaflets remain in a mid-valvular position sealing the mitral orifice, but open abruptly with the start of diastole. The sector scan shows gradual apposition of only the distal tips of the two leaflets during diastole. The major portions of the leaflets appear to close only with the onset of isovolumic contraction shortly after inscription of the R wave. It seems that most of the valve tissue is affected by pressure and not volume changes within the left ventricle.

The mitral valve prolapse syndrome has recently been the subject of two-dimensional echocardiographic study (Gilbert *et al.*, 1976; Millman *et al.*, 1976; Sahn *et al.*, 1976). B-scanning was unable to detect leaflet movement into the left atrium (Millman *et al.*, 1976), and multiple crystal scans visualise only superior systolic arching of the leaflets (Gilbert *et al.*, 1976; Sahn *et al.*, 1976). Though the latter scans were able to detect abnormal systolic arching of the mitral leaflets in patients with prolapse, no posteriorly moving structure was visualised to account for the prominent systolic deformity seen on the TM-echocardiogram. Simple superior movements would not be detected by standard echocardiographic equipment. However, real-time sector scanning has now shown significant superior and posterior movements of redundant mitral leaflet tissue, and confirms mitral prolapse into the left atrium. Because this is a real-time technique, maximal appreciation of the described findings can be achieved only by viewing the videotape. Reproduction of single frames can, at most, provide a reasonable suggestion of the dynamic observations.

Correlation of the standard time motion (Fig. 5) and sector scan (Fig. 4) echocardiograms suggests that motion of the prominent structure immediately behind the central portion of the posterior mitral leaflet (Fig. 4) accounts for the late systolic deformity characteristic of mitral valve prolapse. This structure is felt to be redundant mitral leaflet tissue though this cannot be documented unequivocally. The single angiographic study in this group showed only posterior leaflet prolapse, and no patient has required valve replacement. The cross-sectional area of normal mitral leaflets is 1·5 to 2·2 times greater than the area of the orifice. Therefore, when in the closed position these leaflets must fold as an accordion. Pathological studies of ballooning mitral valves have shown great excesses of tissue (Barlow *et al.*, 1968; Bittar and Sosa, 1968; Trent *et al.*, 1970; Shappell *et al.*, 1973), and, therefore, one would expect this tissue to bunch up in the confined space of the mitral orifice. Though others (Gilbert *et al.*, 1976; Sahn *et al.*, 1976) have not identified similar echocardiographic abnormalities the prolapse patients studied here had very large posterior systolic motion abnormalities of the mitral valve, and at least 4 of the 6 patients had probable myxomatous leaflet degeneration. Thus excess leaflet tissue is not an unexpected observation in this group.

With the onset of systole the redundant mitral tissue is sometimes propelled posteriorly, thus generating a pattern of pansystolic prolapse on the time-motion echocardiogram. More often the posterior motion may be delayed by an initial superior and slightly anterior movement. In the latter situation the standard echocardiogram (Fig. 5) would show only a late systolic prolapse. Regardless of the standard echocardiographic prolapse pattern in the patients studied, it is apparent that the mitral leaflet prolapses into the left atrium for the entire systolic phase of the cardiac cycle. It is not clear why the leaflet motion in some patients is initially superior and anterior, while in others it is posterior. A previous study has shown that both the pansystolic and late systolic prolapse patterns may occur in the same patient (Cohen, 1976). The appearance of a late systolic murmur in many patients with mitral valve prolapse does not diminish the impact of the above conclusions. As pointed out previously (Cohen, 1976) the murmur is generated by blood regurgitating across the mitral orifice into the left atrium. Because the surface area of the leaflets exceeds the size of the orifice, bulging of the leaflets may occur before they separate enough to allow reflux of blood. Thus, prolapse may occur earlier than recorded auscultatory abnormalities might suggest.

The standard echocardiogram of three mitral valve prolapse patients chosen for this study showed multiple systolic echoes with the typical late systolic deformity (Fig. 5). As shown in Fig. 4 the redundant mitral valve tissue at times appeared to be fragmented, with each portion reflecting sound waves. Thus the multiple systolic echoes observed may all originate from a single—the posterior—leaflet. The diagnosis of double mitral leaflet prolapse has been based on the assumption that the most anterior systolic echo with a posterior movement represented motion of the anterior leaflet, while the more posterior echo reflected motion of the posterior leaflet. However, present observations which suggest that all of the multiple abnormal echoes may be from one leaflet imply that the diagnosis of double leaflet prolapse should be made cautiously. Because motion of the anterior leaflet was not well recorded in the patients with prolapse, it is possible that anterior prolapse may also coexist. Better sector scan resolution may help resolve this question.

Real-time echocardiographic imaging, a powerful non-invasive diagnostic tool, has permitted further insight into the pathophysiology of the mitral prolapse syndrome. In at least some patients redundant mitral leaflet tissue may be the primary abnormality in this syndrome. As suggested by Jeresaty (1975) one need not assume that left ventricular contraction abnormalities are responsible for the prolapsing valve syndrome. Mitral valve tissue does prolapse into the left atrium, and in many instances does so for the duration of the systolic phase of the cardiac cycle regardless of the standard time-motion echocardiographic pattern.

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Renal arteriovenous fistula masquerading as severe valvar heart disease

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SUMMARY Two patients with renal arteriovenous fistulae are described, who presented in high output failure. Murmurs were detected in these patients on routine physical examination years before, and when cardiac failure ensued they were assumed to have decompensated valvar heart disease. Full investigation revealed the arteriovenous fistulae and both patients made a good recovery after surgical ligation.

An arteriovenous fistula occurring after abdominal surgery is uncommon and may escape detection, unless the characteristic murmur is sought and angiographic studies performed. We report 2 patients in whom renal arteriovenous fistulae followed nephrectomy and resulted in signs and symptoms consistent with severe valvar heart disease.

Case reports

CASE 1

A 61-year-old woman had a 10-year past history of dyspnoea on exertion. Six years previously a heart murmur had been detected on routine examination. In the following year hypertension was noted, and treatment was started with salt restriction, diuretic, and methyldopa. Four months before admission she developed congestive heart failure and was started on digoxin, but despite this she presented in pulmonary oedema one month later. There was no past history of rheumatism or coronary heart disease, but she had had multiple abdominal surgical procedures, including a right nephrectomy in 1960 for renal tuberculosis and nephrolithiasis.

Physical examination showed a blood pressure of 160/60 mmHg, with a regular pulse of 80 per minute. The carotid upstroke was brisk and full. Lungs were clear. A hyperdynamic apical impulse was palpable in the sixth left intercostal space. A systolic thrill was present, maximal at the lower left sternal border. On auscultation, the first sound was normal, the second sound narrowly split, and aortic closure slightly accentuated. A harsh grade 3/6 midsystolic murmur was loudest in the second right intercostal space; a grade 4/6 continuous murmur was heard over the entire chest posteriorly loudest over the right costovertebral angle, and in the right upper abdominal quadrant anteriorly where a continuous thrill was present. Loud third and fourth sound gallops were also noted. There was no hepatosplenomegaly. Mild oedema of the ankles was present.

The electrocardiogram showed normal sinus rhythm, left atrial abnormality, and increased QRS voltages denoting left ventricular hypertrophy. Chest *x*-ray films showed cardiomegaly with left ventricular and left atrial enlargement and prominent pulmonary vascular markings.

Cardiac catheterisation showed raised right heart pressures. No left or right shunt was detected with the hydrogen electrode. The cardiac output was 10·75 l/min, with cardiac index 6·60 l/min per m^2. There was a wide aortic pulse pressure of 120 mmHg. Left ventricular end-diastolic pressure was raised to 32 mmHg. There was no gradient across the aortic valve. Left ventriculogram showed normal contractility with minimal mitral regurgitation. Ascending aortography showed no aortic regurgitation. The coronary arteries were normal. Abdominal aortogram disclosed a right renal artery fistula to the inferior vena cava (Fig. 1). The fistula was closed at operation. The patient tolerated the procedure well and since then has been asymptomatic. After operation, no murmur has been heard. Chest *x*-ray films have shown a decrease in heart size without congestive changes.

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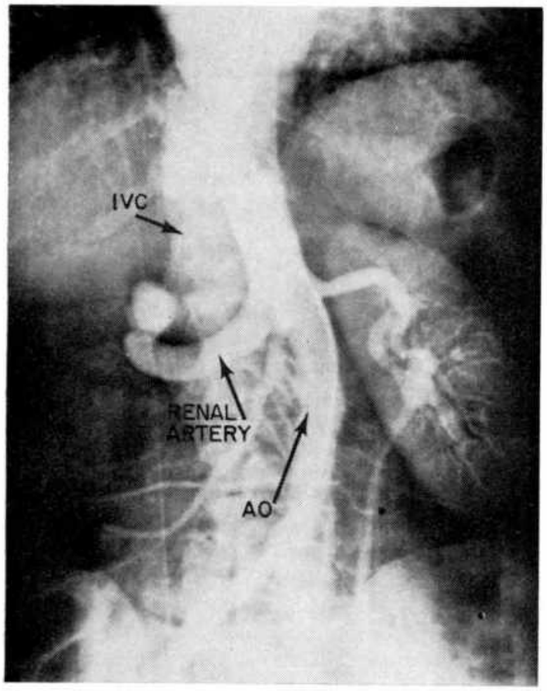

Fig. 1 *Case 1. Abdominal aortogram shows normal aorta (AO). The right kidney is absent. Both renal arteries are seen, with the right renal artery greatly enlarged, and there is immediate filling of the inferior vena cava (IVC) comparable with a central arteriovenous fistula.*

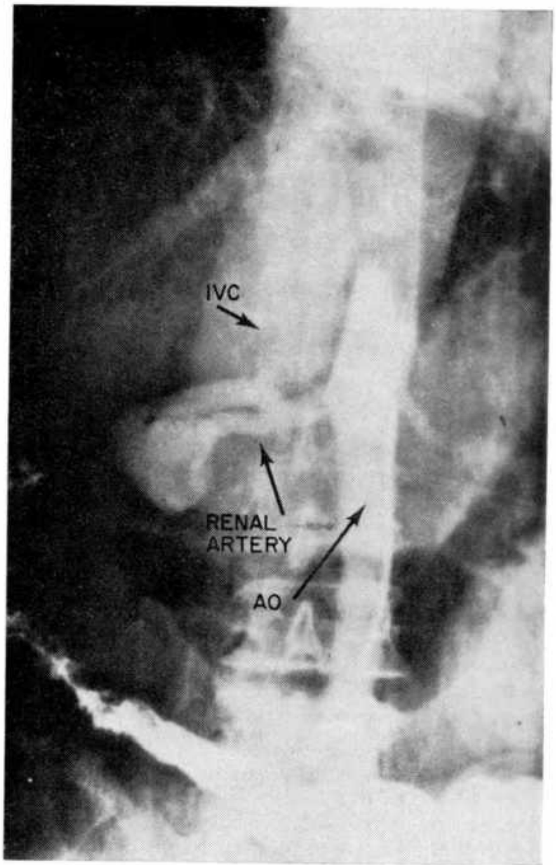

Fig. 2 *Case 2. Abdominal aortogram with catheter in aorta (AO) at level of renal arteries. The right renal artery is enlarged and there is early filling of inferior vena cava (IVC) from tortuous renal artery to inferior vena cava fistula.*

CASE 2

A 66-year-old woman had a right nephrectomy at the age of 26 for renal tuberculosis. Three years before admission, she developed exertional dyspnoea associated with a sensation of pressure in the chest, and on examination a heart murmur was noted. She became more breathless and presented in congestive heart failure with atrial fibrillation. She improved with treatment and was then referred for further evaluation.

On examination the blood pressure was 165/70 mmHg and the pulse regular at 74 per minute. The peripheral pulses were brisk and full. The lungs were clear. A sustained cardiac apical impulse was palpable in the sixth left intercostal space in the anterior axillary line. A systolic thrill was present and maximal at the base. On auscultation, the first sound was normal, and the second sound narrowly split with aortic closure slightly diminished. A grade 5/6 harsh, midsystolic murmur was heard at the second right intercostal space and radiated to the neck, and there was a grade 2/6 descrescendo diastolic murmur at the left sternal border; a grade 4/6 continuous murmur and thrill was maximal in the right upper abdominal quadrant and radiated widely to the chest, back, and praecordium. There was no hepatosplenomegaly and no peripheral oedema.

Electrocardiogram showed normal sinus rhythm, left atrial abnormality, and voltage changes of left ventricular hypertrophy. Chest *x*-ray films showed cardiomegaly with left atrial and ventricular enlargement and increased pulmonary vascularity.

Cardiac catheterisation showed minimal aortic valve calcification. Right heart pressures were raised. Cardiac output was 13·81 l/min, with cardiac index 8·15 l/min per m^2. There was a peak aortic valve gradient of 24 mmHg. Left ventricular end-diastolic pressure was 11 mmHg. Left ventriculogram showed normal contractility, with no mitral regurgitation, and aortogram showed no aortic regurgitation. Selective coronary arteriography showed a proximal 50 per cent stenosis of the left anterior descending artery. Abdominal aortography revealed a large fistula from the right renal artery to the inferior vena cava (Fig. 2). Surgical resection of the fistula was followed by an uneventful recovery. The patient is now asymptomatic and requires no cardiac medications. On examination, there is still a grade 2/6 midsystolic murmur, but without thrill. Chest *x*-ray films showed a decrease in heart size and no pulmonary congestive changes.

Discussion

The diagnosis of arteriovenous fistula may be readily apparent when the history and clinical findings are typical (Gomes and Bernatz, 1970). When a major arterial to venous fistula develops insidiously after earlier surgical intervention, the causative event may not be appreciated and high output cardiac failure may be overlooked. In our patients an erroneous diagnosis of valvar heart disease was made initially, because of the murmurs associated with increased cardiac output. Thus, the significance of the continuous murmur, located remotely from the heart, was not recognised. The finding of a wide pulse pressure, left atrial and left ventricular enlargement on the *x*-ray film, and a diastolic overload pattern of left ventricular hypertrophy on the electrocardiogram appeared to support the misconception that mixed aortic valve disease was the major anatomical defect. Only one such case of a renal arteriovenous fistula mimicking valvar heart disease has been published (Blesa *et al.*, 1976).

Renal arteriovenous fistulae may result from mass ligation of the artery and vein. Such fistulae may develop particularly when transfixing sutures are used which may pass through both structures establishing a potential tract along which a communication can develop (Aravanis *et al.*, 1962). Perioperative infection is another factor implicated in the genesis of surgical arteriovenous fistulae (Gitlitz *et al.*, 1963). The interval between fistula formation and development of high output cardiac failure is variable, with duration and size of shunt the primary determining factors (Shirey, 1959). Onset of symptoms in post-nephrectomy arteriovenous fistula ranges from 5 months to 35 years, with a mean of 15 years (Joseph *et al.*, 1972). In our second patient, there was a 40-year interval between nephrectomy and detection of an arteriovenous fistula.

The physiology of arteriovenous fistula has been extensively studied (Holman, 1923; Krumharr *et al.*, 1974). The abnormal communication between the systemic artery and vein produces a left-to-right shunt with perfusion of a vascular bed with low peripheral resistance. Cardiac output increases as a compensatory mechanism. Because of the run-off through the fistula, the diastolic pressure remains normal or falls, the systolic pressure increases significantly, and the pulse pressure widens. As a result of diastolic overload, cardiomegaly ensues and high output failure develops. Systolic ejection or regurgitant murmurs are accentuated by high output failure, and may therefore mask the presence of an arteriovenous fistula.

Treatment of an arteriovenous fistula consists of primary closure of the artery and vein, and resection of any associated aneurysm (Cummings *et al.*, 1975). When detected, the fistula should be excised before cardiac hypertrophy and failure develop. Prolonged delay in recognition and surgical treatment of an arteriovenous fistula may be followed by only slight decrease in heart size and result in little haemodynamic improvement (Gomes and Bernatz, 1970). In our cases, surgical correction resulted in narrowing of the pulse pressure, decrease in heart size, disappearance of the continuous murmur, and immediate slowing of the heart rate (Branham's sign). In addition, the praecordial flow murmurs decreased and heart failure resolved after ligation of the fistula. Though in our cases cardiac auscultation disclosed systolic and diastolic murmurs associated with increased flow, the continuous murmur was not apparent on praecordial examination but only on auscultation of areas remote from the heart. The increase in murmur intensity on remote examination compared with praecordial auscultation is a clue that a non-cardiac vascular anomaly may be present. This has been previously emphasised as a useful diagnostic sign in peripheral pulmonary stenosis and other extracardiac lesions (Perloff and Lebauer, 1969).

In conclusion, arteriovenous fistula should be suspected in patients with surgical incisions and a continuous murmur. Recognition of a remote continuous murmur heard best over a surgical incision should suggest this unusual cause of insidious congestive heart failure.

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Angina with normal coronary arteriograms

Value of coronary sinus lactate estimation in diagnosis and treatment

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SUMMARY Thirty-five patients with chest pain of sufficient severity to warrant coronary arteriography had normal coronary arteriograms. In each of them coronary sinus lactate was measured before and during atrial pacing. In 16 the lactate metabolism was normal as shown by a change between resting and peak pacing arteriovenous lactate difference of less than 0·09 mmol/l (0·8 mg/100 ml). Nineteen patients had abnormal lactate metabolism, the change being greater than 0·09 mmol/l (0·8 mg/100 ml). Sixteen (84%) of the group with abnormal lactate metabolism responded symptomatically to oral beta-blockade in contrast to only one patient in the normal group ($P < 0{\cdot}001$). After 1 year all 16 patients with abnormal lactate metabolism who had responded to beta-blockade worsened when placebo was substituted. Fifteen of the 16 patients with normal lactate metabolism had become free of symptoms on no specific drug therapy; it is thus unlikely that their original pain was of cardiac origin.

By estimating the coronary sinus lactate, it is, therefore, possible to divide patients with chest pain and normal coronary arteriograms into two groups. Those with pain of non-cardiac origin have normal lactate metabolism, are unlikely to respond to beta-blockade, and improve spontaneously. The group with abnormal lactate metabolism have genuine angina, usually respond to beta-blockade, and deteriorate when treatment is discontinued. Further observation is required to determine the prognosis of the two groups and to estimate the frequency of development of coronary artery disease.

Up to 10 per cent of patients with suspected angina pectoris have normal coronary arteriograms (Kemp *et al.*, 1973). Even when coronary arteries are normal, abnormal electrocardiograms at rest or on exercise and abnormal myocardial lactate metabolism after atrial pacing suggest myocardial ischaemia (Boudoulas *et al.*, 1974; Richardson *et al.*, 1974).

We report here a series of 35 patients with chest pain who had normal coronary arteriograms. All had coronary sinus lactate estimations after atrial pacing to identify the development of anaerobic myocardial metabolism. Their response to treatment was also assessed.

Patients and methods

PATIENTS

Thirty-five patients, 16 men aged 26 to 58 years (mean 46 years) and 19 women aged 21 to 54 years (mean 44 years), were investigated. In each case we considered that the severity of the patient's chest pain warranted invasive investigation and graded the pain as 'definite' or 'uncertain' angina pectoris on our interpretation of the symptoms. No patient had evidence of anaemia, thyroid disease, diabetes mellitus, valvar heart disease, hypertension, or autoimmune disease. Before the investigations beta-blocking drugs had been discontinued for 1 week and digoxin for 2 weeks.

ELECTROCARDIOGRAPHY

A resting 12-lead electrocardiogram was recorded immediately before the radiotelemetric exercise electrocardiogram which was performed under standard conditions (Jackson *et al.*, 1975). ST segment depression in lead V5 was measured before and after exercise. Ischaemia was considered present when there was ST segment depression of at least 1 mm for 0·08 s or more in at least 5 consecutive beats.

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Table 1 *Summary of results*

		Abnormal lactate metabolism (n = 19)	*Normal lactate metabolism (n = 16)*	*P*
Clinical diagnosis	'Definite'	16	3	< 0·001
	'Uncertain'	3	13	< 0·001
Pacing induced angina		17	8	< 0·02
Abnormal electro-cardiogram	Resting	5	2	NS
	Exercise	8	2	NS
	After pacing	13	4	< 0·02

NS, not significant; n, number of patients.

CORONARY SINUS LACTATE PACING STUDY

This was performed as described in the preceding paper (Jackson *et al.*, 1978).

CORONARY ARTERIOGRAPHY

This was performed as described in the preceding paper (Jackson *et al.*, 1978).

Results

These are summarised in Table 1. Statistical analysis employed Student's t test and Fisher's exact test.

CORONARY SINUS LACTATE

Nineteen patients had a change in resting and peak pacing arteriovenous lactate difference greater than 0·09 mmol/l (0·8 mg/100 ml) which we consider is indicative of ischaemia (Jackson *et al.*, 1978). Sixteen patients had normal myocardial lactate metabolism.

CLINICAL DIAGNOSIS

'Definite' angina was present in 19 patients (54%), of whom 16 had abnormal lactate metabolism and 3 normal lactate metabolism (P < 0·001).

ELECTROCARDIOGRAPHY

In 5 of the 19 patients with abnormal lactate metabolism the resting electrocardiogram was abnormal, but is was also abnormal in 2 of the 16 patients with normal lactate metabolism, a total incidence of 20 per cent. Of the 35 patients (30%), 10 had an abnormal exercise electrocardiogram (Fig.), 8 coming from the abnormal lactate group. Of the 35 patients, 17 had abnormal electrocardiograms after pacing (50%) (Parker *et al.*, 1969), 13 of these were in the abnormal lactate group (P < 0·02). Pacing induced angina in a total of 25 (71%) and 17 of these had abnormal lactate metabolism (P < 0·02).

ECHOCARDIOGRAPHY

This was normal in all patients.

Table 2 *Response to treatment*

	Abnormal lactate metabolism (n = 19)	*Normal lactate metabolism (n = 16)*	*P*
Relief of pain by glyceryl trinitrate	15	3	< 0·001
Improvement on treatment with propranolol	16	1	< 0·001
Symptoms after stopping propranolol	16	1	< 0·001

RESPONSE TO TREATMENT

All patients were treated with sublingual glyceryl trinitrate and oral propranolol. The dose of propranolol was increased until optimum beta-blockade was achieved, as defined by reduction of peak exercise heart rate (Jackson *et al.*, 1975). Sixteen patients (84%) within the abnormal lactate group responded to propranolol (Table 2) in contrast to only 1 patient with normal lactate metabolism (P < 0·001). All patients in the abnormal lactate group who responded to oral propranolol had an increase in the frequency of angina when placebo was substituted one year later, whereas 15 of the 16 patients with normal lactate metabolism had become pain free on no specific treatment. The withdrawal of beta-blockade was not associated with any rebound angina. Fourteen

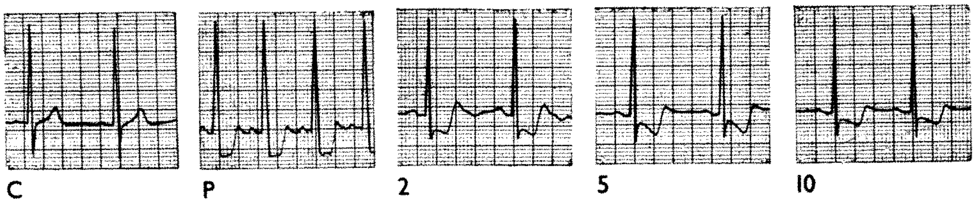

Fig. *Depression of ST segment by exercise in patient with normal coronary arteries. Control (C), maximum ST segment depression during exercise (P), and 2, 5, and 10 minutes after exercise.*

patients (74%) with abnormal lactate metabolism responded to glyceryl trinitrate while only 3 (19%) with normal lactate metabolism did so ($P < 0{\cdot}001$).

Discussion

Typical angina pectoris can occur in patients shown to have normal major coronary arteries on selective coronary arteriography (Kemp *et al.*, 1973; Richardson *et al.*, 1974). Previous studies have identified patients with normal coronary arteries with both abnormal electrocardiograms at rest or on exercise and abnormal lactate metabolism after atrial pacing (Boudoulas *et al.*, 1974; Richardson *et al.*, 1974). We have previously shown that patients with coronary artery disease have a change in resting and peak pacing arteriovenous lactate difference greater than 0·09 mmol/l (0·8 mg/100 ml) and we believe that this indicates the development of anaerobic metabolism (Jackson *et al.*, 1978). By this definition, atrial pacing induced abnormal lactate metabolism in 19 patients.

It has also been shown in patients with coronary artery disease that myocardial lactate metabolism improves, and the time from atrial pacing to pain increases after glyceryl trinitrate (Chiong *et al.*, 1972). We have recently shown that beta-blockers have a similar beneficial effect (Jackson *et al.*, 1977). Of 19 patients with abnormal lactate metabolism, 15 responded to glyceryl trinitrate and 16 to propranolol. In contrast, of 16 patients with normal lactate metabolism only 1 responded to propranolol and 3 to glyceryl trinitrate. Measurement of coronary sinus lactate is thus the most reliable objective means of predicting response to either glyceryl trinitrate or propranolol. It was noteworthy that the patients with abnormal lactate metabolism all worsened when propranolol was withdrawn after 12 months of therapy, whereas all but 1 patient with normal lactate metabolism were free from pain on no specific treatment 12 months after investigation. As most of the patients with normal lactate metabolism had chest pain which had been labelled clinically 'uncertain' angina, it is likely that their pain was not of cardiac origin. We believe that there is now sufficient evidence for us to advocate the routine estimation of coronary sinus lactate before and during atrial pacing in patients with chest pain and normal coronary arteriograms, as there appear to be two distinct groups of patients who differ in their prognosis and response to treatment. While the outlook for patients with genuine angina and normal coronary arteriograms is good (Kemp *et al.*, 1973), further follow-up is still required. It remains to be shown whether patients with angina and normal coronary arteriograms, but with abnormal lactate metabolism, are at risk of developing coronary artery disease.

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Diagnosis of coronary artery disease by estimation of coronary sinus lactate

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SUMMARY In an attempt to assess the value of coronary sinus lactate estimation before and during atrial pacing for the diagnosis of obstructive coronary artery disease, 70 patients with angina were investigated in this way and by selective coronary arteriography. Thirty-five had radiologically normal coronary arteries and 35 had coronary artery disease. When the change in coronary arteriovenous lactate difference was less than 0·09 mmol/l (0·8 mg/100 ml) between the control and the peak atrial pacing sample, the coronary arteries were normal except in one patient who had distal disease of a single vessel. When the change was greater than 0·22 mmol/l (2·0 mg/100 ml) coronary artery disease was always found, and when the change was greater than 0·39 mmol/l (3·5 mg/100 ml) there was always disease of two or three vessels. Unfortunately, the presence or absence of coronary artery disease could not be predicted when the change fell between 0·09 and 0·22 mmol/l (0·8 and 2·0 mg/100 ml). Estimation of coronary sinus lactate before and during atrial pacing can thus frequently distinguish patients with normal coronary arteries from those with coronary artery disease.

The diagnosis of angina pectoris is based upon interpretation of the patient's history. Though most patients with angina pectoris have obstructive coronary artery disease, between 5 and 10 per cent have normal coronary arteries (Kemp *et al.*, 1973). So far, no investigation other than selective coronary arteriography has been able to differentiate these two groups.

In this study we compared the change in level of coronary sinus lactate after atrial pacing with the findings at coronary arteriography. Additional diagnostic information obtained included resting and radiotelemetric exercise-electrocardiograms and fasting lipid estimations.

Patients and methods

PATIENTS

Seventy patients, 46 men and 24 women, aged 26 to 70 years (mean 49 years) were investigated. The clinical diagnosis of angina pectoris was graded as 'definite' or 'uncertain' before beginning investigations. No patient suffered from anaemia, thyroid disease, diabetes, valvar heart disease, or autoimmune disease. Before the investigation beta-blocking drugs were discontinued for 1 week and digoxin for 2 weeks.

ELECTROCARDIOGRAPHY

A resting 12-lead electrocardiogram was recorded immediately before the exercise test which was carried out as previously described (Jackson *et al.*, 1975). Using radiotelemetry, ST segment depression in lead V5 was measured before and after exercise. Myocardial ischaemia was considered to be present when there was ST segment depression of at least 1 mm for 0·08 s or more in at least 5 consecutive beats.

CORONARY SINUS LACTATE PACING STUDY

Myocardial metabolism is normally aerobic, but in the presence of ischaemia anaerobic metabolism develops, resulting in a decrease in lactate extraction by the myocardium. In our studies the coronary arterial lactate was assumed to be the same as that of the femoral artery. The investigation was performed on a separate occasion to coronary arteriography. After the patient had rested for 45 minutes, a Zucker bipolar electrode catheter (Zucker *et al.*, 1965) was inserted into an antecubital vein, and the tip was fluoroscopically positioned 2 cm within the main coronary sinus as viewed in the anteroposterior projection. The position of the tip was

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repeatedly checked by injection of contrast medium. Arterial samples were obtained from the femoral artery through a No. 19G needle inserted under local anaesthesia, and femoral arterial pressure was recorded throughout the study on a Mingograph 81 recorder. Both the venous catheter and arterial needle were intermittently flushed with heparinised saline. Before pacing at least two control samples were taken simultaneously from the coronary sinus and femoral artery. Using a battery-powered pacemaker (Devices) the heart rate was increased at 5-second intervals by increments of 10 beats per minute. The peak pacing rate was at least 10 beats above the peak exercise rate or the maximum predicted heart rate (Lange Andersen *et al.*, 1971), whichever was the greater, and was discontinued as soon as the patient experienced his usual chest discomfort or pain of a severity that would stop him in his normal daily life. Blood samples were taken at peak pacing and at 2, 5, and 10 minutes after cessation of pacing. Electrocardiograms were taken throughout the study. Lactate was estimated by Livesley's (Livesley and Atkinson, 1974) modification of Hohorst's method. Myocardial extraction ratio is defined as the difference between arterial and coronary sinus lactate, divided by arterial lactate, and expressed as a percentage. At peak pacing, myocardial ischaemia is indicated by either a lactate extraction ratio of less than 10 per cent or a coronary sinus lactate greater than the arterial lactate (Cohen *et al.*, 1966). A change in coronary arteriovenous lactate difference of greater than 0·09 mmol/l (0·8 mg/100 ml) between control samples and samples at peak pacing has previously been considered to indicate the presence of coronary artery disease (Livesley and Oram, 1973) and we have compared this measurement with the lactate extraction ratio.

ANGIOCARDIOGRAPHY

Selective coronary arteriography was performed by either the Sones or the Judkins technique using 76 per cent or 85 per cent meglumine/sodium diatrizoate mixtures, and recorded in a single plane on 35 mm film at 50 frames a second using a Siemens H type intensifier system. Left ventriculography was performed in the right anterior oblique position. The angiograms were interpreted on two separate occasions without knowledge of the results of the other investigations. Patients with coronary artery disease were grouped according to the presence of at least 50 per cent narrowing in 1, 2, or 3 major vessels. The left ventricle was considered abnormal if the ejection fraction was less than 50 per cent or localised akinesia or dyskinesia was present.

LIPIDS

Fasting plasma lipids were estimated on 3 separate occasions and were considered pathological when the cholesterol was greater than 6·50 mmol/l (250 mg/100 ml) and/or triglycerides greater than 1·70 mmol/l (150 mg/100 ml), with or without electrophoretic abnormalities.

BLOOD PRESSURE

Five of the 70 patients had hypertension as defined by a diastolic pressure greater than 100 mmHg on 3 separate occasions after the patient had been resting supine for 5 minutes. In all, this was essential hypertension.

COMPLICATIONS

There were none throughout the study.

Results

A summary of clinical and electrocardiographic findings is shown in Table 1 and the results of

Table 1 *Clinical and electrocardiographic data*

	Normal coronary arteries		*Coronary artery disease*		
	Change in arteriovenous lactate difference on pacing		*No. of diseased arteries*		
	< 0·8 mg/100 ml	*> 0·8 mg/100 ml*	*1*	*2*	*3*
No. of patients	16	19	6	13	16
Clinical diagnosis of angina					
'Definite'	3	17	6	12	16
'Uncertain'	13	2	0	1	0
Abnormal resting electrocardiogram	2 (13%)	5 (26%)	1 (16%)	5 (38%)	15 (94%)
Abnormal exercise electrocardiogram	2 (13%)	8 (42%)	2 (33%)	8 (61%)	11 (69%)
Mean exercise ST depression (mm)	0·13 ± 0·1	0·7 ± 0·2	0·6 ± 0·4	0·85 ± 0·3	1·53 ± 0·4
Abnormal resting and/or exercise electrocardiogram	3 (19%)	12 (63%)	2 (33%)	11 (85%)	15 (94%)
Abnormal pacing electrocardiogram	4 (25%)	13 (68%)	2 (33%)	9 (69%)	12 (75%)
Mean peak pacing ST depression (mm)	0·5 ± 0·2	0·7 ± 0·2	0·75 ± 0·5	1·15 ± 0·25	1·75 ± 0·3

For conversion from traditional units to SI units: Lactate 1 mg/100 ml ≏ 0·111 mmol/l.

Table 2 *Lactate measurements in patients with healthy and diseased coronary arteries*

	Normal coronary arteries		*Coronary artery disease*		
	Change in arteriovenous lactate difference on pacing		*No. of diseased arteries*		
	< 0·8 mg/100 ml	*> 0·8 mg/100 ml*	*1*	*2*	*3*
No. of patients	16	19	6	13	16
Mean control minus peak pacing lactate arteriovenous difference (mg/100 ml)	0·15 ± 0·1	1·16 ± 0·04	0·93 ± 0·3	2·3 ± 0·3	3·3 ± 0·7
Mean lactate extraction ratio % on peak pacing	27·6 ± 2·9	10·7 ± 2·81	26·9 ± 4·3	− 0·1 ± 5·9	−18·6 ± 13·5
Abnormal lactate metabolism 2 minutes after stopping pacing	0	9 (47%)	4 (66%)	10 (77%)	16 (100%)
Mean arterial lactate (mg/100 ml)	6·2 ± 0·4	7·0 ± 0·5	6·98 ± 0·9	7·69 ± 0·6	7·6 ± 0·7
Lactate production (i.e. coronary sinus lactate more than femoral arterial)	0	0	0	6 (46%)	10 (62%)

For conversion from traditional units to SI units: Lactate: 1 mg/100 ml ≏ 0·111 mmol/l.

lactate measurements are given in Table 2. Patients were divided into two main groups, those with normal coronary arteries and those with one or more stenoses of more than 50 per cent in at least one major coronary artery. Patients with normal coronary arteries were subdivided into 2 groups based on a change in arteriovenous lactate difference greater or less than 0·09 mmol/l (0·8 mg/100 ml) between control and peak pacing samples. Patients with coronary artery disease were subdivided into those with disease of 1, 2, or 3 vessels. Non-parametric statistical tests were used to evaluate the significance of the correlations between the variables. These included the χ^2 goodness of fit test for contingency tables, the Mann-Whitney U-test, Spearman's coefficient of rank correlation, and the Kruskal-Wallis one-way analysis of variance.

CORONARY AND LEFT VENTRICULOGRAPHY

Thirty-five patients had normal coronary arteries and 35 had coronary artery disease. Of the latter group, 16 had significant disease of 3 arteries, 13 of 2 arteries, and 6 of a single artery. Abnormal left ventricular function was found in 5 patients, all with coronary artery disease, 4 of whom had disease of all 3 vessels. Fifty-seven per cent of patients with normal coronary arteries and 97 per cent with coronary artery disease had typical angina pectoris.

ELECTROCARDIOGRAPHY

Resting electrocardiograms showed ischaemia in 7 patients with normal coronary arteries (20%) and in 21 patients with coronary artery disease (60%). After exercise a further 8 patients with normal coronary arteries developed abnormal electrocardiograms, making a total of 15 (43%). In those with coronary artery disease, the number of patients with abnormal electrocardiograms rose after exercise testing from 21 to 28 (80%).

The more extensive the coronary artery disease the more likely a patient was to have an abnormal resting electrocardiogram ($P < 0·01$). Furthermore, the more extensive the coronary artery disease the greater was the degree of ST segment depression induced by exercise ($P < 0·05$). However, it is clear that electrocardiography alone fails to differentiate between patients with normal coronary arteries and those with coronary artery disease, as not only is the electrocardiogram frequently normal in the presence of coronary artery disease, but also it may be abnormal in the absence of coronary artery disease. Neither the presence nor the degree of ST segment depression after atrial pacing differentiated between the two groups.

CORONARY SINUS LACTATE

We found that a change in coronary arteriovenous lactate difference between the control and the peak pacing samples of more than 0·09 mmol/l (0·8 mg/100 ml) correlated with a lactate extraction ratio of less than 10 per cent ($P < 0·001$) in patients with normal coronary arteries and in those with coronary artery disease. There is very little to choose between these methods of expressing lactate abnormalities. An arteriovenous lactate difference of less than 0·09 mmol/l (0·8 mg/100 ml) was associated with normal coronary arteries in all but one patient who had a single distal lesion of the circumflex artery (Table 3).

No patient with normal coronary arteries had an arteriovenous lactate difference of more than 0·22 mmol/l (2·0 mg/100 ml). In the range 0·09 to 0·22 mmol/l (0·8 mg to 2·0 mg/100 ml) there were patients both with and without coronary artery disease. A change in arteriovenous difference greater than 0·39 mmol/l (3·5 mg/100 ml) was

Table 3 *Correlation between abnormal lactate metabolism on atrial pacing and extent of coronary artery disease*

Control minus peak pacing arteriovenous lactate difference (mg/100 ml)	*No. of diseased arteries*			
	0 (*n* = *35*)	*1* (*n* = *6*)	*2* (*n* = *13*)	*3* (*n* = *16*)
0-0·8 mg (0-0·09 mmol/l)	16	1	0	0
0·8-2·0 (0·09-0·22 mmol/l)	19	4	7	8
2·0-3·5 (0·22-0·39 mmol/l)	0	1	4	1
> 3·5 (> 0·39 mmol/l)	0	0	2	7

n = no. of patients.
For conversion from traditional units to SI units: Lactate: 1 mg/100 ml ≏ 0·111 mmol/l.

diagnostic of disease of 2 or 3 vessels. Thus the extent of the coronary artery disease paralleled the degree of change in arteriovenous lactate difference on pacing ($P < 0{\cdot}001$). The presence of abnormal lactate metabolism for 2 minutes after cessation of atrial pacing did not differentiate between patients with normal coronary arteries and those with coronary artery disease. Only in the presence of coronary artery disease did lactate production on atrial pacing result in coronary sinus levels greater than arterial.

PLASMA LIPID PROFILES

These were abnormal in 14 per cent of patients with normal coronary arteries and in 66 per cent of those with coronary artery disease. Abnormal fasting lipids correlated significantly with the extent of coronary artery disease ($P < 0{\cdot}05$) but were not significantly related to changes in the electrocardiogram, coronary sinus lactate changes, or any other variable.

Since the lipid abnormalities did not seem to be related to the change in arteriovenous lactate difference on pacing, and since both were independently significantly correlated with the severity of coronary artery disease, it seemed likely that when both were abnormal this would more reliably predict coronary artery disease. In fact, we found that patients with both raised plasma lipids and abnormal coronary sinus lactate on atrial pacing were more likely to have coronary artery disease than when only one of these was abnormal ($P < 0{\cdot}005$).

Discussion

Typical angina pectoris can occur in patients shown to have normal major coronary vessels on selective coronary arteriography (Kemp *et al.*, 1973). Fifty-seven per cent of our patients with normal coronary arteries and 97 per cent of those with coronary artery disease had clinically typical angina. The presence of anginal pain does not, therefore, necessarily imply the presence of coronary artery disease.

Measurement of coronary sinus lactate before and after atrial pacing stress can determine the presence or absence of anaerobic metabolism under these conditions and, subject to certain anatomical limitations, is the most reliable means of assessing this (Gorlin, 1969). We have assessed the value of coronary sinus lactate estimation in predicting the presence or absence of coronary artery disease. Though the procedure is invasive it can be performed on an outpatient basis and in our hands has not been associated with any morbidity or mortality. Though a previous study suggested that the presence of abnormal lactate metabolism after atrial pacing was diagnostic of coronary artery disease, coronary arteriographic proof was not obtained (Livesley and Oram, 1973). Furthermore, abnormal myocardial lactate metabolism on atrial pacing has also been shown in the presence of normal coronary arteries (Boudoulas *et al.*, 1974; Richardson *et al.*, 1974). In this study, we therefore correlated the coronary angiographic findings with the abnormalities of lactate metabolism. All patients with a change in arteriovenous lactate difference of less than 0·09 mmol/l (0·8 mg/100 ml) on pacing had normal coronary arteries with the exception of one who had localised distal disease of one artery. This illustrates the limitation of sampling the main coronary sinus in the presence of localised regional ischaemia (Herman *et al.*, 1967); the normal result in the presence of distal disease probably reflects dilution of the lactate from the ischaemic myocardium by the venous blood from the larger aerobic zones. All patients with a control minus peak pacing arteriovenous lactate difference of greater than 0·22 mmol/l (2·0 mg/100 ml) had coronary artery disease but a difference between 0·09 and 0·22 mmol/l (0·8 and 2·0 mg/100 ml) did not distinguish between those with normal coronary arteries and those with coronary artery disease.

The conclusion is that the estimation of coronary sinus lactate before and after atrial pacing is a reliable method of demonstrating the presence of extensive coronary artery disease when the control minus peak pacing arteriovenous lactate difference is greater than 0·22 mmol/l (2 mg/100 ml); additionally, the absence of clinically important coronary artery disease can be assumed when the change is less than 0·09 mmol/l (0·8 mg/100 ml). However, if the change is between 0·09 and 0·22 mmol/l (0·8 and 2·0 mg/100 ml) this finding alone is not diagnostic of coronary artery disease, but when the lipids are abnormal the presence of coronary artery disease is more likely. The association of increased lipid levels with abnormal lactate metabolism may provide a useful screening test for the detection of coronary artery disease.

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Comparison of interventricular septal motion studied by ventriculography and echocardiography in patients with atrial septal defect[1]

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SUMMARY Abnormal systolic interventricular septal motion is an echocardiographic manifestation of right ventricular volume overload. In order to determine the anatomical basis for this echocardiographic finding, septal motion recorded by left lateral or left anterior oblique ventriculograms was compared with echocardiographic ventricular septal motion. Thirteen patients with secundum atrial septal defects and 7 control patients with trivial or no heart disease were included in the study. We found that on ventriculograms the systolic motion of the interventricular septum was similar in both atrial septal defect and control patients. That is, the cephalic third of the septum moved anteriorly in systole in 9 of the 13 patients with atrial septal defect and in 3 of the 7 controls. The caudal two-thirds of the septum moved posteriorly in all patients. These results are compatible with the theory that argues that the echocardiographic abnormalities of septal motion in patients with atrial septal defect result from an end-diastolic septal flattening or bowing of the septum into the cavity of the left ventricle.

Abnormal systolic interventricular septal motion is a cardinal echocardiographic sign in patients with intra-atrial septal defects (Popp *et al.*, 1969; Diamond *et al.*, 1971). Clinical and experimental studies have suggested that right ventricular volume overload is the cause of abnormal interventricular septal motion (Kerber *et al.*, 1973). There are 3 major hypotheses that attempt to explain the echocardiographic abnormalities of interventricular septal motion in right ventricular volume overload. The first is that with regard to a fixed reference point (location of the echocardiographic transducer on the chest wall), the net motion of the septum will be anterior in systole if there is an anterior motion of the entire heart caused by the ejection of a large right ventricular volume (Meyer *et al.*, 1972; Pearlman *et al.*, 1976). The second hypothesis suggests that in patients with right ventricular volume overload there is caudal displacement of the normal septal 'hinge point' (the point about which the septum pivots, as ventricular ejection occurs), so that a much larger than usual portion of the septum moves anteriorly (Hagan *et al.*, 1974). The third hypothesis holds that the interventricular septum may bow into the cavity of the left ventricle at end-diastole to accommodate the right ventricular volume overload. Starting in early systole, when the ventricle begins to assume a more rounded configuration, the septum may appear to move anteriorly (Weyman *et al.*, 1976).

The purpose of this study was to use a non-ultrasonic technique, ventriculography, to evaluate the motion of the interventricular septum in patients with intra-atrial septal defects, and to correlate the results with standard M mode echocardiographic examination, in order to assess critically the hypotheses listed above.

Methods

PATIENT SELECTION

The records of all patients undergoing catheterisation at Iowa University Hospitals with a diagnosis of intra-atrial septal defect during the period 1 March 1974 to 1 November 1976 were reviewed. All patients who met the following criteria were included in this study: (1) Ostium secundum intra-atrial septal defect; (2) availability of cardiac catheterisation data including a left ventriculogram

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taken in the left anterior oblique or left lateral projection; (3) availability of a good quality echocardiographic recording of interventricular septal motion at the level of the mitral valve chordae; (4) lack of significant pulmonary hypertension (pulmonary artery systolic pressure less than 35 mmHg); (5) lack of other significant or complicating haemodynamic abnormalities, for example mitral regurgitation (Popp *et al.*, 1969; Diamond *et al.*, 1971). All the patients had 'incomplete right bundle-branch block', but none had other conduction defects such as left bundle-branch block or pre-excitation syndromes. None of the patients had previous cardiac surgery or coronary artery disease. Thirteen patients with intra-atrial septal defects met these criteria. The patients who were used as controls were selected on the following basis: (1) discharge diagnosis of no heart disease or trivial haemodynamic defect; (2) availability of cardiac catheterisation data including a left ventriculogram taken in the left anterior oblique or left lateral projection; (3) availability of a good quality echocardiographic recording of interventricular septal motion at the chordal level.

VENTRICULOGRAMS

The left ventricular cineangiograms were performed in the 45 to 60° left anterior oblique or the left lateral projection at 60 frames per second. The ventriculograms of 8 patients with intra-atrial septal defect were obtained in the left anterior oblique projection and 5 were obtained in the left lateral projection. Of the control patients, 4 ventriculograms were obtained in the left anterior oblique and 3 in the left lateral projection. The ventriculograms were projected and the ventricular silhouettes drawn superimposed at end-systole and end-diastole. The vertebral bodies were visible on all the cineangiograms and therefore were used as fixed reference points; thus, anterior and posterior interventricular septal motion refer to motion away from or toward the vertebral bodies, respectively. The interventricular septum was divided into thirds by drawing a line from the junction of the aortic valve ring and the interventricular septum to the most caudal point on the diastolic ventricular silhouette. This line was then divided into thirds. We defined the ventriculographic hinge point as that point at which the end-systolic silhouette of the interventricular septum intersected with the end-diastolic silhouette.

Ventricular silhouettes were drawn of one of the first three beats after injection of contrast. No important change in ventricular volume or function would have occurred (Hammermeister and Warbasse, 1973).

ECHOCARDIOGRAMS

Echocardiographic examinations were performed using a Smith Kline Ekoline 20A ultrasonoscope interfaced with a Honeywell strip chart recorder. A 2·25 MHz focused transducer was used for adults and a 3·75 MHz transducer was used for smaller children. Echocardiograms were recorded with standard techniques, that is the transducer was placed parasternally and perpendicular to the chest wall in the third or fourth left intercostal space. The patient was supine or in the left lateral decubitus position. In all the patients and controls the mitral valve was identified; then the transducer was directed inferiorly to the level of the chordae tendineae. At this level the determination of systolic interventricular septal motion was made.

Interventricular septal motion was considered to be normal on echocardiography if the left side of the interventricular septum moved posteriorly, that is toward the left ventricular posterior wall during systolic ejection, and abnormal if it moved anteriorly during systolic ejection (type A), or had no anterior-posterior movement during ejection (type B) (Diamond *et al.*, 1971). In most patients an echocardiographic 'sweep' from the chordal level to the aortic root was performed and we determined whether an echocardiographic hinge point was present. We defined this hinge point as that point about which the septum appeared to rotate with the superior portion moving anteriorly in systole and the inferior portion moving posteriorly with systole, as shown in Fig. 1. This determination was made in 10 of the patients with intra-atrial septal defects and in 4 of the controls. The remaining 6 echocardiograms (3 patients and 3 controls) did not contain a technically adequate recording of the sweep from the base to the apex of the ventricle. That is, though the interventricular septal motion was recorded well at the chordal level, it was not recorded sufficiently far superiorly or inferiorly to that point so that a directional difference in the systolic interventricular septal motion at different levels along the septum might be identified.

Results

PATIENTS SELECTED

The characteristics of the patients in this study are listed in the Table. The age range of the patients with intra-atrial septal defects was from 1 year to 35 years; 11 of these patients were female. The ratio of pulmonary to systemic blood flow ($\dot{Q}p/\dot{Q}s$) ranged from 2·2:1 to 4·4:1. The patients who served as controls ranged in age from 6 to 35 years, and 5 of these 7 were male. Four of the control patients had small interventricular septal defects

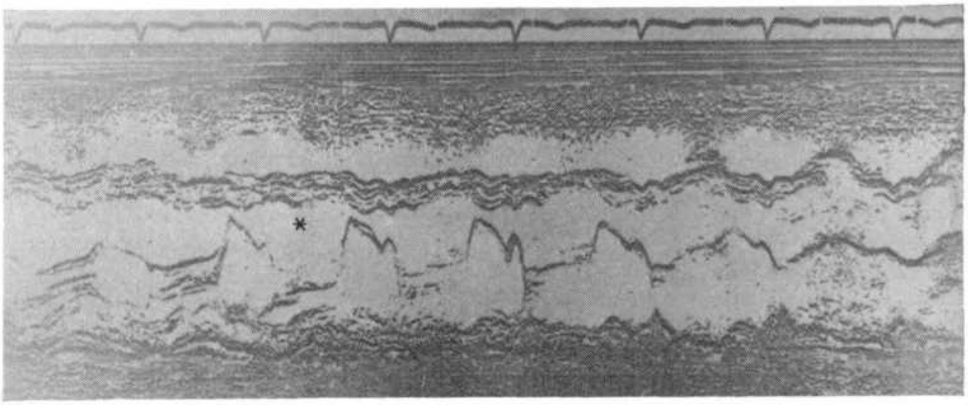

Fig. 1 *Normal patient. An echocardiographic sweep from the level of the chordae tendineae to the aorta is shown. The systolic motion of the interventricular septum is posterior at the chordal level and anterior when the beam is directed at and superior to the mitral valve. The point of transition from posterior to anterior septal motion (*) was considered the echocardiographic hinge point.*

with left to right shunts having a $\dot{Q}$p/$\dot{Q}$s ratio of 1·5:1 or less. One patient had minimal pulmonary stenosis with a gradient of 12 mmHg at rest. One patient had a very mild mitral prolapse with a trivial amount of mitral regurgitation and one patient had no evident cardiac disease.

ECHOCARDIOGRAMS

All of the control patients had normal interventricular septal systolic motion. A hinge point was seen in all 4 of the echocardiograms that were technically adequate to analyse for this feature (Fig. 1). In all 4 the hinge point was observed above the level at

Table

Patient	*Age*	*Sex*	*$\dot{Q}p/\dot{Q}s$**	*Echo†*	*Hinge point Echo*	*Hinge point Ventriculogram*
Intra-atrial septal defect						
Studied in left anterior oblique						
1	20	F	3:1	B	No	No
2	35	F	3:1	B	Yes	No
3	22	F	3·4:1	A	No	Yes
4	26	F	2·6:1	A	No	Yes
5	33	F	4:1	N	—	Yes
6	29	M	3·7:1	A	No	Yes
7	25	M	2·6:1	A	No	Yes
8	22	F	4·2:1	A	No	Yes
Studied in left lateral						
9	1 yr	F	2·9:1	N	—	No
10	2	F	2·9:1	B	—	Yes
11	12	F	2·7:1	A	No	Yes
12	4	F	2·2:1	A	No	No
13	12	F	4·4:1	A	No	Yes
Control patients						
Studied in left anterior oblique						
14	32	F	Small VSD Qp/Qs 1·4 :1	N	—	Yes
15	35	M	Small VSD Qp/Qs 1·2:1	N	Yes	No
16	18	M	Small VSD Qp/Qs 1·5:1	N	Yes	Yes
17	26	F	Small VSD Qp/Qs 1·2:1	N	Yes	No
Studied in left lateral						
18	6	M	Minimal PS gradient 12 mmHg	N	—	Yes
19	6	M	Normal heart	N	Yes	No
20	17	M	Mitral prolapse, mild mitral regurgitation	N	Yes	No

*Pulmonary flow (Qp)
Systemic flow (Qs)

†A, anterior systolic septal motion; B, lack of systolic septal motion; N, normal posterior systolic septal motion.

VSD, interventricular septal motion; PS, pulmonary stenosis.

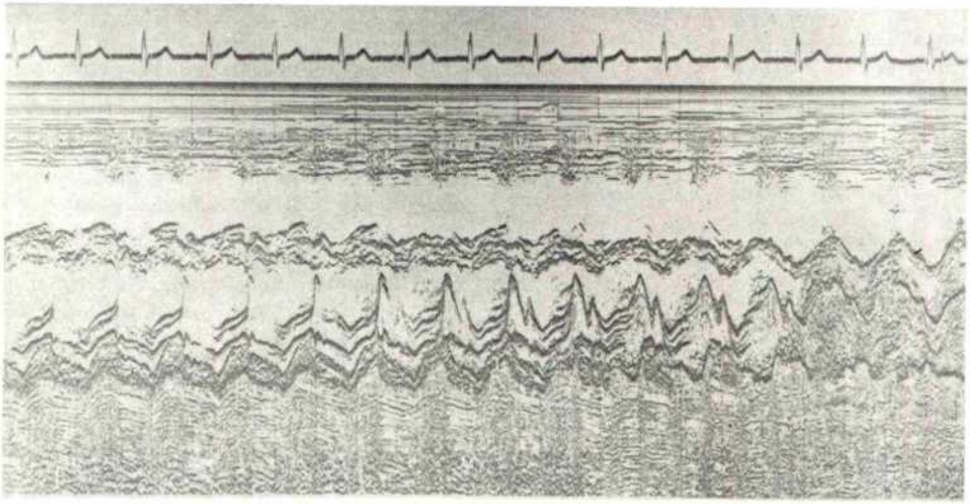

Fig. 2 *Patient with intra-atrial septal defect. An echocardiographic sweep from the chordae to the aorta shows that the entire septum moves anteriorly in systole. No hinge point is seen.*

which the chordae tendineae were recorded. None of the control patients had any abnormality on their echocardiograms except for 1 patient, case 20, who had very slight systolic posterior bowing of the mitral valve leaflets suggesting mitral valve prolapse.

Of the 13 patients with intra-atrial septal defects, 11 had abnormal systolic interventricular septal motion. Eight had type A motion (Diamond *et al.*, 1971); that is the left ventricular side of the interventricular septum moved anteriorly or toward the chest wall during systole. Three patients had no net systolic interventricular septal motion and were classified as type B. Two patients had normal systolic interventricular septal motion, a finding occasionally encountered in patients with intra-atrial septal defect, and apparently not closely correlated with the volume of the shunt (McCann *et al.*, 1972; Kerber *et al.*, 1973). A hinge point could be identified in only 1 of the 10 patients with intra-atrial septal defect who had a technically adequate echocardiogram for this determination. In this patient, who had type B septal motion, the echocardiographic hinge point appeared to be below the level of the chordae tendineae. In the remaining 9 patients with intra-atrial septal defect, the entire visualised septum from the chordae to the aortic root appeared to move anteriorly by echocardiography (Fig. 2).

VENTRICULOGRAMS

In all of the controls and the patients with intra-atrial septal defect, the ventriculographic motion of the caudal two-thirds of the interventricular septum was always posterior in systole, whether the ventricle was viewed from the left lateral or the left anterior oblique projection. In 9 of the 13 patients with intra-atrial septal defect and 3 of the 7 control patients a ventriculographic hinge point was observed. In the remaining ventriculograms no hinge point was seen. Examples are seen in Fig. 3. Cephalic to the hinge point, the interventricular septum moved anteriorly in systole. However, the level of this ventriculographic hinge point was at or superior to the junction of the cephalic and middle thirds of the septum in all ventriculograms in which it was observed, and no difference in interventricular septal motion was noted between the control patients and the patients with intra-atrial septal defect. Furthermore, the presence of an angiographic hinge point did not correlate with the presence of an echocardiographic hinge point or with the presence of abnormal septal motion at or below the level of the mitral valve chordae seen on the echocardiograms (Table).

Discussion

The major findings in this study are: (1) there is no evident difference in systolic interventricular septal motion seen in left anterior oblique or left lateral ventriculograms between the patients with intra-atrial septal defect and the control subjects; (2) angiographically, the caudal two-thirds of the interventricular septum moved posteriorly during systole in both patients with intra-atrial septal defect and in control subjects, even when there was obvious anterior systolic movement of the inter-

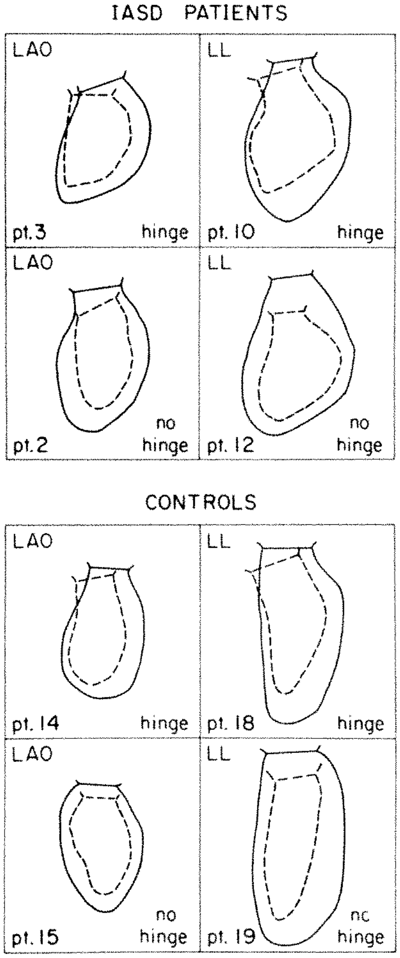

Fig. 3 *This figure shows representative end-diastolic (solid line) and end-systolic (broken lines) silhouettes from ventriculograms of patients with intra-atrial septal defect and controls. Examples from the left anterior oblique (LAO) and the left lateral (LL) projections are shown. A hinge point is present in some patients with atrial septal defect and in some controls, and absent in others. The inferior two-thirds of the septum moves posteriorly in systole in all examples, whether or not a hinge point is present.*

ventricular septum seen below the mitral valve level on echocardiograms; (3) a hinge point was seen angiographically in 9 of 13 patients with atrial septal defect and in 3 of 7 control subjects, and in none of these was it located below the cephalic third of the septum, even in those patients who had obvious echocardiographic anterior systolic interventricular septal motion well below the chordal level. Thus, the presence of an angiographic hinge point did not appear to be related to an echocardiographic hinge point.

How can these discrepancies be explained? The standard echocardiogram and the left anterior oblique or left lateral ventriculogram do not record interventricular septal motion in the same way. The echocardiogram records only a single small area of the interventricular septum at any one transducer position. Moreover, as the septum moves during the cardiac cycle, the portion of the interventricular septum reflecting the beam may change so that the end-systolic sampling is not necessarily from the same area as the end-diastolic sampling. The ventriculogram, though recording a larger portion of the septum, is a silhouette technique. It records in profile and, therefore, may not discern movements of small portions of the interventricular septum, especially if there is an irregular shape or infolding of the interventricular septum along its long axis. The relation of the views of the septum by echocardiogram and by left anterior oblique and left lateral ventriculograms can be seen in Fig. 4. The left anterior oblique ventriculogram appears to profile the interventricular septum more accurately than the left lateral. The lateral view was included in our study because, in state of right ventricular volume overload, the enlarged right ventricle may displace the heart such that the interventricular septum is oriented more nearly parallel to the frontal

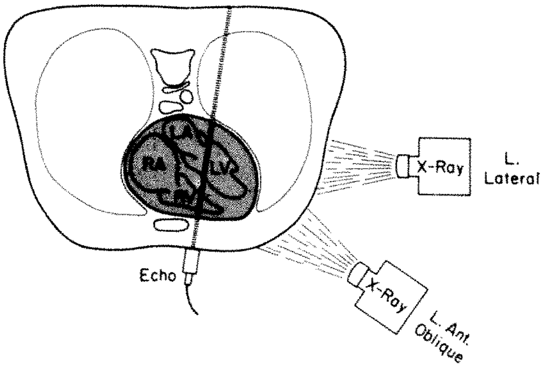

Fig. 4 *For comparison, the angles of view of the echocardiographic transducer and the left lateral and left anterior oblique ventriculograms are drawn. The echocardiogram records only a small portion of the ventricular septum, and the area from which the beam reflects may change during cardiac contraction because of motion and rotation of the heart in systole. Ventriculography visualises the septum by a silhouette technique. The left anterior oblique projection profiles the ventricular septum best in a normal heart. However, there may be rotation of the heart in right ventricular volume overload so that the septum becomes more nearly parallel to the frontal plane and is best profiled in the left lateral projection.*

plane (Meyer *et al.*, 1972). It can be seen from examining Fig. 4 that, in either angiographic view, if the interventricular septum moves towards the vertebral bodies the septal movement is posterior in the saggital plane, though the vector of interventricular septal motion may be directed slightly to the right or left.

Three hypotheses have been advanced to explain the echocardiographic findings of abnormal anterior systolic interventricular septal motion in patients with intra-atrial septal defect. The first of these explains abnormal motion by attributing it to an artefact which occurs because the right ventricle is considerably enlarged and displaces the left ventricle posteriorly. During cardiac contraction the entire heart moves anteriorly because of the ejection of a large right ventricular volume (Fig. 5). Therefore, even though the left ventricular side of the interventricular septum is actually contracting normally and moving toward the free posterior wall of the ventricle, with respect to the transducer, the net motion is anterior. This theory has been proposed by Meyer *et al.* (1972) and appears to be supported by the more recent work of Pearlman *et al.* (1976). The theory presupposes concentric left ventricular contraction and would also require very exaggerated anterior motion of the left ventrivular posterior wall during systole, which would occur if the entire heart's anterior motion were sufficient to cause the net interventricular septal motion to be anterior. However, we did not find anterior systolic motion of the interventricular septum angiographically but we did find net posterior systolic movement of at least the lower two-thirds of the left side of the interventricular septum with respect to a fixed radiological reference point in all of our patients with intra-atrial septal defects, as well as in all the control subjects. Moreover, there did not appear to be exaggeration of the posterior wall motion on ventriculograms of the patients with intra-atrial septal defects compared with the controls (Fig. 2).

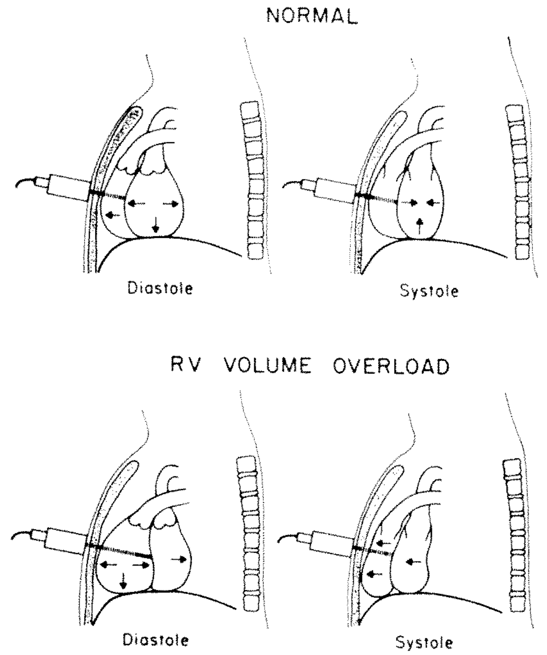

Fig. 5 *This figure illustrates the hypothesis that paradoxical septal motion occurs because the entire heart is displaced posteriorly in diastole in right ventricular volume overload (lower left panel), and with ejection of the large right ventricular volume the entire heart swings anteriorly, producing anterior motion with respect to the echocardiographic transducer (lower right). The left ventricle would contract concentrically, and if this theory were correct there would be exaggerated anterior systolic motion of the posterior left ventricular wall. The normal situation is illustrated at the top for comparison.*

The second hypothesis stems from the work of Hagan and colleagues (1974) who used a multi-element ultrasonic transducer to obtain a long axis cross-sectional cardiac image. They described an echocardiographic hinge point in the interventricular septum. Interventricular septal motion by this technique appeared to be anterior in the cephalic third of the septum and posterior in the middle and caudal thirds in normal subjects. In patients with right ventricular volume overload, the point at which the septum appeared to pivot occurred below the junction of the cephalic and middle thirds of the interventricular septum. Presumably the motion of the entire heart is altered in a similar fashion as shown in Fig. 6. A hinge point was inconstantly present on the ventriculograms which we reviewed, and, even when present, never occurred below the junction of the cephalic and middle thirds of the interventricular septum. Another difference between our angiographic findings and the data obtained with the multi-element transducer is that 8 of the 21 patients with right ventricular volume overload examined with the multi-element ultrasound technique seemed to have anterior systolic motion of the entire portion of the interventricular septum that could be recorded with this transducer. However, on ventriculography, we invariably found posterior systolic motion of the inferior two-thirds of the interventricular septum. Movement of the heart about a hinge point on its long axis could account for the anterior motion of the cephalic third of the interventricular septum seen angiographically in some of our patients (Fig. 3). Moreover, the hinge point

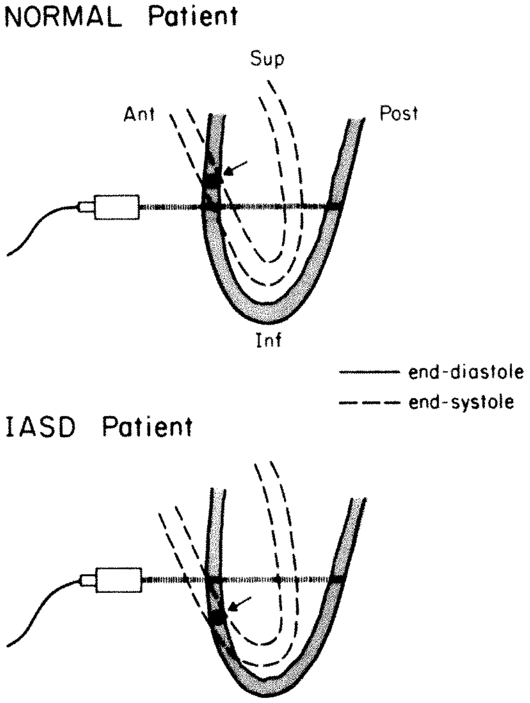

Fig. 6 *The hypothesis explaining anterior systolic septal motion by an inferior displacement of a hinge point (marked with a dot and arrow) is illustrated in the figure. The septum appears to move posteriorly in systole in normal patients (upper panel), but anteriorly in right ventricular volume overload (lower panel), because the hinge point has been displaced inferiorly. IASD = intra-atrial septal defect.*

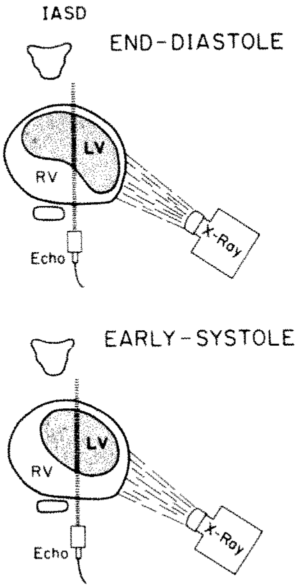

Fig. 7 *This figure shows a possible explanation for the discrepancies between echocardiographic and ventriculographic demonstration of septal motion in right ventricular volume overload. End-diastolic bowing of the septum into the cavity of the left ventricle may occur in right ventricular volume overload as shown in a transverse view in the upper panel. In the lower panel the ventricle has begun to assume a rounded configuration in early systole. This alteration in ventricular shape may not be recorded in the silhouette of the ventriculogram because contrast medium in the far right and left anterior portions of the ventricular cavity may overlie and conceal the diastolic septal invagination with respect to the* x-ray *beam. Thus, the septum may appear to move anteriorly in systole with respect to the ultrasound beam, but posteriorly in systole with respect to the silhouette visualised radiographically.*

hypothesis may be correct if it is combined with another hypothesis, that of an irregular shape of the septum in atrial septal defect patients (see below).

The third hypothesis, proposed by Weyman *et al.* (1976), is based on evidence gathered from analysis of minor axis cross-section echocardiograms obtained with a mechanical sector-scanner. Weyman and his co-workers showed that in right ventricular volume overload the interventricular septum flattens or bows inward into the cavity of the left ventricle at end-diastole. During the early part of systole, the minor axis cross-section begins to reassume a rounded configuration. Later in systole a relatively concentric contraction ensues. This pattern of contraction is shown diagrammatically in Fig. 7. Our findings are compatible with this mechanism in that invagination of the septum into the left ventricular cavity might not appear on a left lateral or left anterior oblique ventriculogram as abnormal septal motion. As can be seen in Fig. 7, interventricular septal flattening or invagination into the cavity of the left ventricle might be obscured by angiographic contrast medium in the anterior portion of the left ventricle overlying the area of invagination with respect to the *x*-ray beam, thereby forming a silhouette that would not show this localised deformity. Moreover, the finding of end-diastolic septal flattening or bowing in the ventricular minor axis is compatible with the finding of a septal hinge point in the long axis. That is, the portion of the septum which bows inward at end-diastole appears to move anteriorly in early systole as the ventricle assumes a rounded configuration. The lowest point of the invagination appears as an inferiorly displaced hinge point. However, this rationale does not explain the uniform finding by Hagan *et al.* of a hinge point in the cephalic portion of the septum in normal subjects. It may be that normal people have some flattening or bowing of the interventricular septum in end-diastole but only in the most cephalic portion. Our data are consistent with the fact that the heart might also rotate about a point on its cephalo-caudal axis in some patients.

Popio *et al.* (1975) studied angiographic ventricular motion in patients with intra-atrial septal defect by motion analysis of left anterior oblique cineventriculograms along the major axis and along three minor axes. They, therefore, did not study motion with respect to a fixed reference point but rather with respect to a line bisecting the ventricle along its long axis. They found complex multiphasic motion in the midportion of the interventricular septum in midsystole and net contraction of both the septal and posterior walls toward the centre of the ventricle. These findings are compatible with our own, and the multiphasic motions of the interventricular septum in midsystole may be a reflection of the complex motions involved in the reassumption of a rounded minor-axis contour of the ventricle after the interventricular septum has been flattened or bowed into the left ventricular cavity at end-diastole.

We conclude that the abnormal anterior systolic motion of the interventricular septum in patients with intra-atrial septal defect is not found in ventriculographic recordings of interventricular septal motion. In both the patients with intra-atrial septal defect and controls the caudal two-thirds of the interventricular septum, as seen angiographically, move posteriorly in systole. This information favours the hypothesis which holds that the interventricular septum flattens or bows into the left ventricular cavity at end-diastole in conditions of right ventricular overload, and that this anatomical alteration is responsible for the abnormality of interventricular septal motion seen on echocardiography.

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Case against routine use of glyceryl trinitrate before coronary angiography[1, 2]

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SUMMARY Changes in coronary artery tone are often neglected in the angiographic assessment of patients with chest pain. To determine the contributions of dynamic coronary artery diameter changes to the degree of coronary narrowing, 47 consecutive chest pain patients were studied without premedication by analysing selective coronary angiograms before and after glyceryl trinitrate. Proximal coronary diameters were measured in superimposed frames with callipers. Lumen diameter increased after glyceryl trinitrate 15 ± 2 per cent in the left main, 18 ± 2 per cent in the left anterior descending, 16 ± 2 per cent in the circumflex, and 17 ± 2 per cent in the right coronary arteries (all $P < 0{\cdot}01$). One hundred and nineteen coronary artery narrowings of < 90 per cent were measured (narrowings > 90 per cent were excluded because of measurement inaccuracy). Of 81 narrowings < 50 per cent, 24 became ≥ 50 per cent because of dilatation of the adjacent region. However, the diameter of the narrowed segment also changed significantly after glyceryl trinitrate, increasing in 28 and decreasing in 3. Of the 28 obstructions which dilated after glyceryl trinitrate, 4 were clinical and angiographic examples of coronary arterial spasm. In 4 other coronary arteries with only outline irregularities before glyceryl trinitrate a localised narrowing (25 to 50%) was seen after glyceryl trinitrate as the proximal artery dilated. We concluded that the routine use of glyceryl trinitrate before coronary angiography alters the measured degree of coronary artery narrowing and obscures the angiographic interpretation.

When nitrates are given before coronary angiography, the coronary artery image often appears enhanced. For this reason, sublingual glyceryl trinitrate has been used routinely before coronary angiography in many laboratories (Baltaxe *et al.*, 1973; Bennett, 1976; Chahine and Luchi, 1976). Some have suggested that the angiographically observed dilatory response of normal coronary arteries differs quantitatively from diseased arteries (Gensini *et al.*, 1971). This raises questions relating to the interpretation of nitrate-induced dilatation of diseased and non-diseased sections of the coronary artery as seen angiographically. Different dilator responses in these areas could distort the angiographic estimate of the degree of coronary artery narrowing. Additionally, recent interest in the role of coronary arterial spasm in the pathogenesis of myocardial ischaemia suggests that spasm may be more common than generally recognised (Bennett, 1976; Chahine and Luchi, 1976; Weiner *et al.*, 1976). Routine use of glyceryl trinitrate before or at the start of an angiographic procedure could have a profound influence on the angiographic interpretation in this setting. Accordingly, the purpose of this study was to assess the effect of glyceryl trinitrate on the angiographic interpretation of coronary artery narrowing.

Methods

Studies were made on 47 consecutive, unpremedicated patients undergoing preoperative evaluation for chest pain. Patients did not receive nitrates for at least 2 hours before the study.

The coronary angiographic procedure was conducted according to standard techniques. Aortic pressure and electrocardiographic leads were constantly monitored.

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ANGIOGRAPHIC AND MEASUREMENT TECHNIQUES

Selective coronary injections of Renografin 76 (TM) were made by hand in multiple projections before (before GTN) and after sublingual glyceryl trinitrate (GTN), 0·4 mg. High quality coronary cineangiograms at 60 frames/s were obtained using 4½ or 6 in image intensification and a 100 mm overframing lens with Ilford Type CF film. The resolution in our two catheterisation laboratories is 2·8 and 3·0 line pairs/mm. Patient position was the same, before and after GTN. This was accomplished by measuring the cardiac apex to table top distance (RAO) or cradle angle (LAO). Similarly, relations between focal spot, patient, and image tube height were kept constant. Because of possible transient vasodilatory effects of Renografin 76 (TM), a minimum of 5 minutes was allowed between coronary injections (Hattenhauer and Neill, 1975).

Selected cineframes from before and after GTN arteriograms were matched for the same part of the cardiac cycle. End-diastolic frames were chosen so that maximal coronary diameters could be analysed. Cineframes were projected on a viewing screen (Tagarno, Model 3500). Coronary artery size was determined by measuring the diameters of the 4 major proximal coronary arteries and coronary narrowings with calipers to the nearest 0·5 mm. Proximal coronary arteries were measured at branch points and narrowings at their minimal diameter. Diameter measurements from control angiograms (before GTN) were then compared with diameter measurements of the same portion of the coronary artery on the GTN angiogram. We found that the projected diameter of a coronary narrowing less than 1·0 mm could not be measured accurately. Therefore, those narrowings (generally 90% or greater) were not included in this report. The degree of narrowing was expressed as a percentage of coronary narrowing. The latter was calculated from the ratio of the diameter at the narrowing to the diameter of the coronary artery immediately proximal to the narrowing × 100.

REPRODUCIBILITY AND SPONTANEOUS VARIATION OF CORONARY ARTERY MEASUREMENTS

The ability to reproduce measured projected image diameters was evaluated by the following studies. Multiple measurements of projected diameters of intracardiac or intra-aortic catheters, proximal coronary arteries, and coronary artery narrowings were made from cineangiographic sequences. For each of these, 25 to 35 individual measurements were made from sequential frames of five to six sequences. Coefficients of variation for each measurement were calculated. Variation of measurements of the same projected diameter (i.e. catheter tip) served as an internal control.

Additionally, in 5 other patients possible spontaneous changes in coronary artery diameter were evaluated by repeating the coronary angiography studies 30 to 60 minutes after the control series of angiograms and before administration of GTN. Eighteen proximal coronary arteries were evaluated in this manner.

Means and standard errors of the mean and coefficients of variation (Snedecor and Cochran, 1973) were calculated for the measured diameters and their ratios. Student's 't' test was used to determine the statistical significance of the difference between the mean values of before GTN and GTN observations. A P value $< 0{\cdot}05$ was considered statistically significant.

Results

MEASUREMENT REPRODUCIBILITY AND SPONTANEOUS VARIATION IN CORONARY ARTERY DIAMETER

The mean value for measurements of the projected diameter of aortic catheters in 5 patients ranged from 4·5 to 8·0 mm and their respective coefficients of variation ranged from 0 to 5 per cent. The projected mean diameter of 6 coronary arteries ranged from 8 to 12·5 mm as their respective coefficients of variation ranged from 0 to 3 per cent. The projected mean diameters of 5 coronary narrowings ranged from 3 to 5 mm as their respective coefficients of variation ranged from 0 to 7 per cent. Coronary diameter measurements repeated after 30 to 60 minutes without GTN showed that one coronary artery decreased in size, 16 remained unchanged, and 1 enlarged. The net change was an increase of 2 ± 3 per cent (mean ± standard error); $P > 0{\cdot}05$.

EFFECT OF GLYCERYL TRINITRATE ON CORONARY ARTERY MEASUREMENTS

Effects on proximal coronary arteries

One-hundred and sixty-nine proximal coronary artery diameters were measured before and after GTN. These diameters increased as follows: left main 15 ± 2 per cent, anterior descending branch 18 ± 2 per cent, circumflex branch 16 ± 2 per cent, and right coronary artery 17 ± 2 per cent (all $P < 0{\cdot}01$). There was no significant difference in the degree of changes induced by GTN between the 4 arteries studied. The dilator effect was not related to the size of the artery or the presence or absence of coronary artery disease. There was pronounced individual variability both in magnitude and direction of the changes. Exclud-

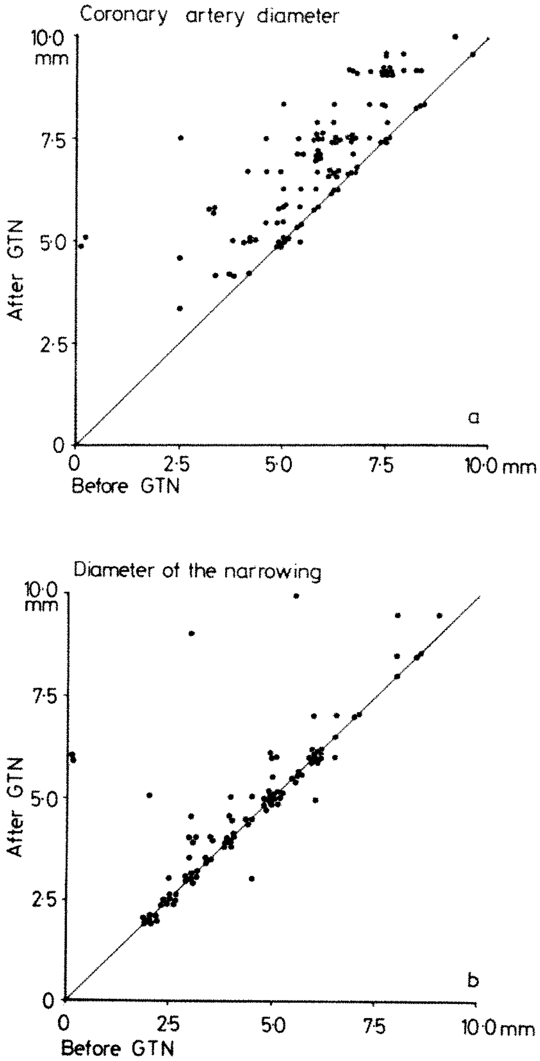

Fig. 1a and b *Effect of GTN on the diameter of the projected proximal coronary arteries* (a) *and diameter of the coronary narrowing* (b). *Measurements from the before GTN angiogram (horizontal axis) and after GTN (vertical axis) are compared. The solid line represents the line of identity. Dilatation after GTN is represented by points above the identity line. The majority of the major proximal vessels dilate (panel* a) *while the majority of narrowings do not change diameter (panel* b).

ing instances of definite coronary arterial spasm, the diameter changes ranged from a 6 per cent decrease to a 57 per cent increase. The diameter of one proximal artery decreased, 24 arteries remained unchanged, and 144 arteries increased. These coronary responses are summarised in Fig. 1a.

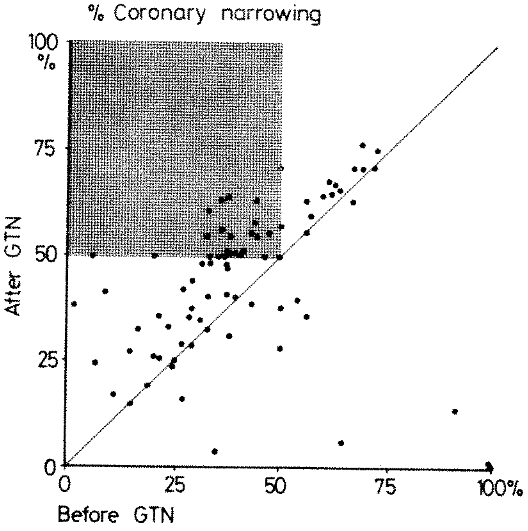

Fig. 2 *Effect of GTN on percentage coronary narrowing. The percentage coronary narrowing, before GTN (horizontal) is compared with a percentage narrowing after GTN (vertical). In most cases, the degree of narrowing increased after GTN. Points lying below the line of identity may represent coronary arterial spasm. The subgroup included in the hatched area (upper left quadrant) represents narrowings measuring < 50 per cent before GTN and > 50 per cent after GTN.*

Effect of glyceryl trinitrate on coronary artery narrowings

Changes in diameter of the 119 coronary narrowings measured are summarised in Fig. 1b. Three narrowings decreased in diameter, 88 remained unchanged, and 28 increased.

Effect of glyceryl trinitrate on percentage narrowing

The influence of GTN on the diameter of the coronary narrowings relative to the diameter of the proximal arteries is shown in Fig. 2. Overall, glyceryl trinitrate produced a small (8% mean) but significant ($P < 0 \cdot 01$) increase in percentage narrowing. Variability was apparent as the percentage narrowing of 15 obstructions decreased, 17 remained unchanged, and 87 increased. Changes in the percentage narrowing were observed for all geometric types and degrees of obstruction. The subgroup of narrowings measuring less than 50 per cent diameter reduction before GTN were of particular interest. Eighty-one narrowings were in this subset. Of these narrowings, 24 showed an apparent increase to 50 per cent narrowing or greater after GTN (stippled area of Fig. 2). The increase in the degree of narrowing of the obstruction within this subset ranged from 4 to 30 per cent.

Effect of glyceryl trinitrate on haemodynamic measurements

After the administration of sublingual GTN mean aortic blood pressure decreased 10 mmHg (average ($P < 0{\cdot}05$), range 4 to 15 mmHg. Heart rate increased 6 beats/min (average $P < 0{\cdot}05$), range 0 to 11 beats/min.

Discussion

Although glyceryl trinitrate is routinely administered before coronary angiography in many laboratories (Baltaxe *et al.*, 1973; Bennett, 1976; Chahine and Luchi, 1976), its precise effects on coronary arteries and arterial narrowings is unclear. Furthermore, its influence on the interpretation of coronary angiograms has not been reported previously.

Our results indicate that a small increase in the degree of coronary narrowing (8% mean) and the proximal coronary diameter (17% mean) occurs after glyceryl trinitrate. Though statistically significant, these changes were not predictable in the individual patient. Gensini and co-workers (1971) using isosorbide dinitrate made similar observations. In our patients, the change in degree of coronary narrowing after sublingual glyceryl trinitrate was

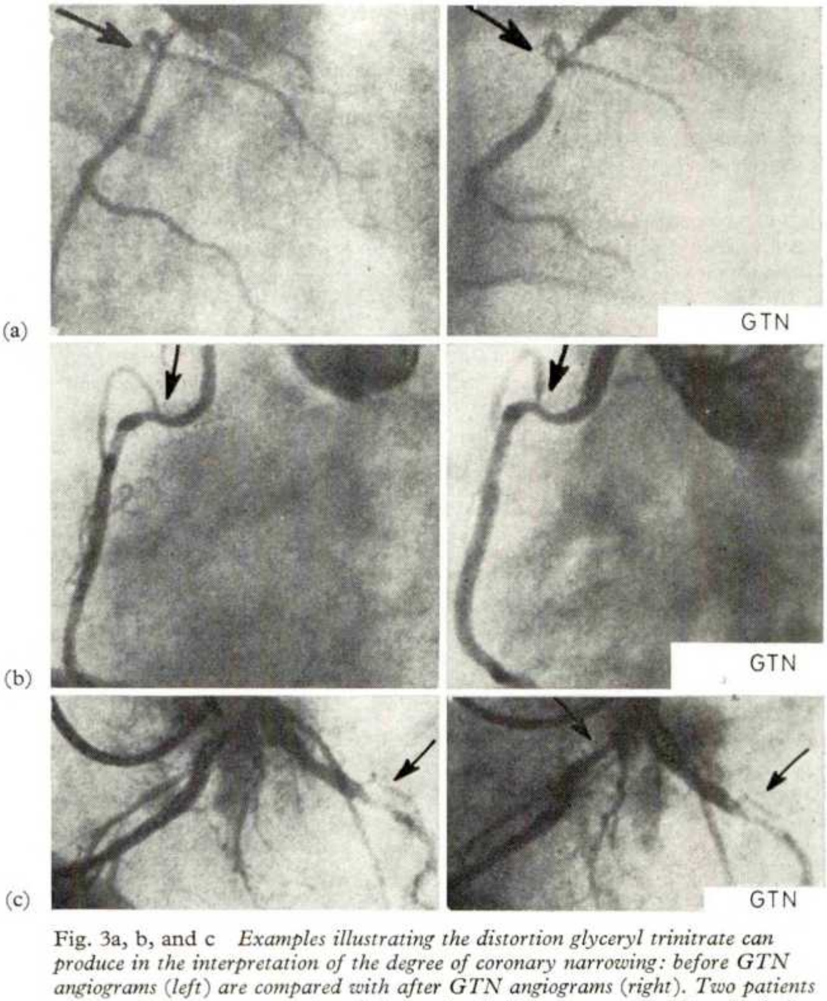

Fig. 3a, b, and c *Examples illustrating the distortion glyceryl trinitrate can produce in the interpretation of the degree of coronary narrowing: before GTN angiograms (left) are compared with after GTN angiograms (right). Two patients with < 50 per cent narrowing of the proximal right coronary (LAO projection),* panel a *and* b, *and another with two < 50 per cent narrowings of the left coronary (LAO projection), panel* c, *are shown. In each case after GTN, disproportionate dilatation of the adjacent vessel relative to the narrowed segment (arrow) caused an apparent increase in the degree of narrowing.*

largely the result of dilatation of the proximal coronary artery relative to the narrowing. An important clinical implication relative to this observation is that approximately one-third of the narrowings measuring $<$ 50 per cent before glyceryl trinitrate, measured $\geqslant$ 50 per cent after glyceryl trinitrate (Fig. 2, stippled area). While few cardiologists would consider these narrowings clinically significant before glyceryl trinitrate, many would interpret them as significant obstructions after glyceryl trinitrate. Several such narrowings measured less than 25 per cent before the drug but measured $\geqslant$ 50 per cent after it. Examples of this type of change are illustrated in Fig. 3. Consideration of the influence of glyceryl trinitrate on the angiographic interpretation, in terms of the number of coronary arteries with significant obstruction, also has important consequences. Because of this differential dilator effect, the routine administration of glyceryl trinitrate would have added at least one additional significant narrowing (50% or greater) in 14 of the 47 (30%) study patients. Additionally, of the 16 patients whose angiograms showed significant obstruction of only one or two major coronary arteries before glyceryl trinitrate, 5 (31%) advanced to 2- or 3-vessel disease, respectively, after administration. Four areas that appeared as trivial lumen outline irregularities on control angiograms became areas of definite 25 to 50 per cent narrowing after glyceryl trinitrate (these narrowings are represented by points lying along the vertical axis of Fig. 2).

The coronary artery narrowings that increased in size also merit comment considering recent interest in the role of coronary artery spasm in the pathophysiology of myocardial ischaemia. In this regard, 28 of 119 narrowings enlarged after glyceryl trinitrate (Fig. 1b). Of these, at least 4 were considered to be examples of coronary spasm. However, many of the other 24 narrowings may represent combinations of atherosclerosis (fixed obstruction) and spasm (reversible obstruction). Alternatively, they could also represent localised atherosclerotic-type changes that do not involve the entire circumference of a vessel.

One patient developed an unexpected response after glyceryl trinitrate as illustrated in Fig. 4 (Feldman *et al.*, 1978). The patient had a history of typical angina pectoris but had no symptoms throughout the study. After sublingual glyceryl trinitrate, new areas of narrowings appeared in the mid-portion of his large right coronary artery. The narrowings persisted, despite sublingual administration of additional 0·4 mg glyceryl trinitrate tablets. At present, we have no reasonable explanation for this unexpected response to the drug but have seen 2 additional patients with similar responses since the completion of this study. In the latter cases, the narrowings after glyceryl trinitrate appeared in the mid-right coronary in one patient and the mid-left anterior descending in the other patient.

Selective coronary angiography after glyceryl trinitrate has an adjunctive role in the evaluation of patients with chest pain. Often, vessels distal to high grade obstructions and coronary collaterals are better visualised after administration of nitrates. In

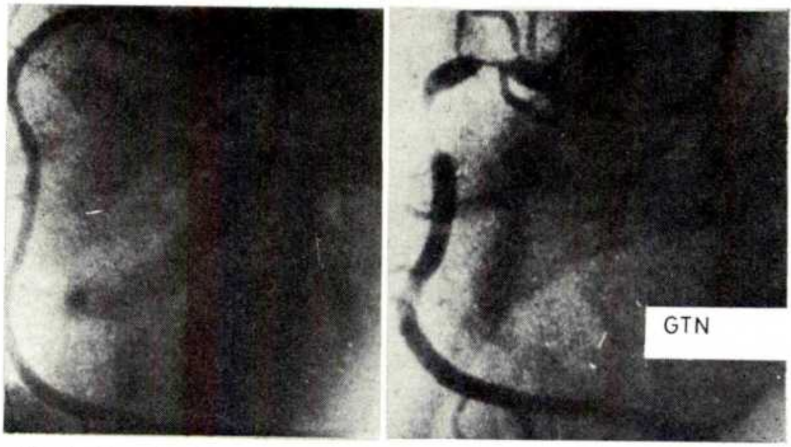

Fig. 4 *Example of an unexpected response observed after GTN. Note proximal and distal vessel dilatation after GTN (right) but areas of narrowing appear which were not apparent before GTN (left). Repeated angiograms after additional 0·4 mg GTN tablets to a total dose of 1·2 mg showed no change. (Reproduced by permission of* American Journal of Cardiology.)

addition, glyceryl trinitrate can help to distinguish fixed narrowings from those with superimposed spasm (Gensini, 1975; Chahine and Luchi, 1976). In patients with coronary narrowings on routine angiograms, another set of arteriograms after glyceryl trinitrate seems appropriate in order to have an improved assessment of possible dynamic changes (Chahine and Luchi, 1976). However, since part of the risk of coronary arteriography is related to the length of the procedure, sound judgement dictates the type of study for each individual patient.

The observations reported here are valid only if the methods are reproducible and accurate and the coronary artery diameter is stable throughout the catheterisation procedure. Reproducibility and accuracy can be accomplished by controlling patient and equipment position, using high quality cineangiographic techniques, and making calibrated measurement with a low coefficient of variation. In our unpremedicated patients, there was no significant change in coronary artery diameter over a 30 to 45 minute period provided the patient did not experience spontaneous angina. During spontaneous chest pain, however, there may be associated changes in coronary size, as we observed and as others have suggested (Weiner *et al.*, 1976).

The methods used include other pertinent limitations. First, coronary artery diameter measurements were made only at specific coronary artery sites; since measurements were not made over the entire coronary artery, we cannot exclude possible diameter changes occurring in other areas. Second, though high quality cineangiography was used, the borders of high degree narrowings (usually $\geqslant$ 90% and measuring $\geqslant$ 1 mm) were at times indistinct; therefore, measurements from these areas were excluded from this report. Third, since measurements were not made in a blind manner, some degree of subjectivity could be associated with the calliper measurements.

In conclusion, these observations indicate that administration of glyceryl trinitrate before coronary angiography can alter the interpretation of the coronary angiogram. This alteration consists of changes in percentage narrowing of the vessel. In most cases, disproportionate dilatation of the vessel adjacent to a narrowing is responsible for these changes. In some patients, however, distinct changes also occur at the narrowing. Some of these changes may represent coronary spasm that could have been obscured if glyceryl trinitrate had been given before the angiogram.

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Comparison of atenolol with propranolol in the treatment of angina pectoris with special reference to once daily administration of atenolol

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SUMMARY Fourteen patients with angina pectoris completed a double blind trial of atenolol 25 mg, 50 mg, and 100 mg twice daily and propranolol 80 mg thrice daily. In comparison with placebo, all active treatments significantly reduced anginal attacks, consumption of glyceryl trinitrate, resting and exercise heart rate, resting and exercise systolic blood pressure, and significantly prolonged exercise time. There was no significant difference between the effects of propranolol and atenolol.

Nine patients completed a further trial comparing atenolol given once or twice daily. Both regimens were effective and there was no significant difference between the reductions in anginal attacks, glyceryl trinitrate consumption, systolic blood pressure, or heart rate. Twenty-four-hour ambulatory electrocardiograms showed that atenolol consistently reduced heart rate throughout the 24-hour period whether given once or twice daily.

Atenolol is a potent antianginal agent which, in most patients, is likely to be effective once daily.

The use of adrenergic beta-receptor antagonists is well established in the treatment of patients with angina pectoris. In general there should be little effective difference between individual agents provided optimum peak exercise heart rate reduction is achieved in each 24-hour period (Jackson *et al.*, 1975b). The possession of intrinsic sympathomimetic activity (ISA) by a beta-blocking agent may, however, be a disadvantage because of a reduced effect on exercise heart rate (Caruthers *et al.*, 1976). In contrast, cardioselective properties may be advantageous to the small number of patients in whom non-selective agents such as propranolol predispose to bronchospasm (Stephen, 1966).

Atenolol is a cardioselective beta-blocking agent without intrinsic sympathomimetic activity (Åström, 1975), which has been shown in volunteers to produce blockade of exercise-induced tachycardia for at least 24 hours after single oral doses (Harry, 1977). The objectives of the present investigations were to compare the effects in patients with stable angina pectoris of graded doses of atenolol with those of a standard effective dose of propranolol (Jackson *et al.*, 1975a). This comparative study was randomised and double blind. In addition, using 24-hour ambulant electrocardiographic monitoring techniques a double blind comparison was also made between optimum doses of atenolol administered once and twice daily.

Patients and methods

SELECTION OF PATIENTS

Patients with exercise-induced angina were selected. They were excluded if the angina was associated with anaemia (haemoglobin < 13 g/dl), valvar heart disease, cardiac failure, obstructive airways disease, cardiac infarction in the previous 3 months, hypertension (fifth-point resting diastolic pressure over 100 mmHg), diabetes, or thyroid disease. In all patients the angina had been stable for more than 3 months and all showed electrocardiographic abnormalities either at rest or on exertion, but no evidence of conduction defects. Chest *x*-ray pictures were normal. No other drugs were used except for glyceryl trinitrate. All patients were clearly informed of the nature of the study and all gave written consent without inducement (Ormrod, 1968). Fourteen patients aged 43 to 57 (mean 53) years entered the study; 12 were men and 2 were women.

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Dosage and regimen

(i) DOUBLE BLIND COMPARISON OF ATENOLOL WITH PROPRANOLOL

Each patient received placebo on a single-blind basis for 4 weeks. They were then allocated to 4 fully randomised monthly treatment periods—atenolol 25 mg twice daily; atenolol 50 mg twice daily; atenolol 100 mg twice daily; and propranolol 80 mg thrice daily. All the preparations were in identical tablets, each dose being 2 tablets. The tablets were taken at 8 am, 2 pm, and 8 pm. For each time a separate tablet container was provided, and each patient was instructed on the importance of taking the correct tablets at the appropriate time. This enabled us to provide a 2 pm placebo dose for the atenolol periods making them indistinguishable from the thrice daily propranolol. Each drug course was checked by counting the trial tablets and glyceryl trinitrate tablets; blood and urine levels were not estimated. Glyceryl trinitrate was supplied in bottles of 100 tablets and replenished monthly.

(ii) DOUBLE BLIND COMPARISON OF ATENOLOL ONCE DAILY WITH ATENOLOL TWICE DAILY ADMINISTRATION

Of the original 14 patients, 9 entered and completed this additional study. The optimum individual dose of atenolol was based on the results of the graded comparison of atenolol with propranolol previously described. In a double blind randomised crossover design patients received either once or twice daily atenolol for one month at each level. The morning and evening tablets were stored in separate containers so that when once daily atenolol was being given at 8 am an identical placebo was given at 8 pm, thereby maintaining the double blind nature of the study. The total daily dosage of atenolol was the same for each patient, thus a patient receiving 200 mg once daily would receive 100 mg twice daily. All the preparations were identical tablets, each dose being two tablets. Each drug course was checked by counting the trial tablets and tablets of glyceryl trinitrate.

PLACEBO MEDICATION PERIODS

The initial design of the present study included a randomised double blind placebo period. However, new evidence published at the time this trial started indicated that the rapid withdrawal of beta-blocking agents might exacerbate angina pectoris and induce myocardial infarction (Diaz *et al.*, 1973; Nellen, 1973; Slome, 1973; Miller *et al.*, 1975). A double blind placebo period was not, therefore, felt to be ethically justified and it was omitted from the present trial. All comparisons of active drug and placebo periods are, therefore, between a single blind placebo run-in period and randomised double blind active treatment periods. The efficacy of each active beta-blocking agent may, therefore, be exaggerated when compared with placebo because of a beneficial natural history change. This would not, however, detract in any way from the randomised double blind comparison of graded doses of atenolol with a known effective dose of propranolol (Jackson *et al.*, 1975a).

Assessment

The patients were seen at fortnightly intervals. At each visit the anginal attack rate and consumption of glyceryl trinitrate were assessed from simple record cards. Glyceryl trinitrate was used only for pain and not prophylactically. Only the records of the second two weeks of each monthly period were compared to avoid carry-over effects (Jackson *et al.*, 1975a). In addition, at each attendance, the supine heart rate was estimated from the electrocardiogram, a standard sphygmomanometer was used for blood pressure recordings, and a full clinical examination was carried out. Any side effects were noted.

In the atenolol versus propranolol study at the end of each 4-week period the patient was weighed and exercised. In the fourth week of the once daily and twice daily atenolol trial the patient underwent 24-hour ambulatory tape recording of his electrocardiogram (Avionics tape recorder system) to allow heart rate to be determined hourly throughout the 24 hours and also minimum and maximum heart rates to be determined and compared with events in the patient's record card. At the end of the study patients were asked directly which month's treatment they preferred.

Exercise test

In 9 patients a step and wall bar test was used, the methodology of which has been described in detail elsewhere (Jackson *et al.*, 1975a). Five patients were exercised upright using a bicycle ergometer. This was calibrated in kpm/min and was pedalled steadily at about 60 rpm (range 45 to 75). The load was increased by 150 kpm/min every 3 minutes until angina occurred. The initial work load was chosen so that each patient experienced angina during the second level (3 to 6 minutes) of exercise.

All data are combined and expressed as exercise time in seconds. Patients were exercised until they experienced the onset of anginal pain or were too breathless to continue. Radiotelemetry with the electrode in the V5 position was used to record resting and exercise heart rates from the electro-

Table 1 *Mean (± SE of mean) anginal attack rate and glyceryl trinitrate consumption (number of tablets) in each treatment period*

	Placebo	*Atenolol* *25 mg twice daily*	*Atenolol* *50 mg twice daily*	*Atenolol* *100 mg twice daily*	*Propranolol* *80 mg thrice daily*
Anginal attacks in last 2 weeks	35 ± 12	25 ± 9	17 ± 5	18 ± 4	14 ± 4
Glyceryl trinitrate consumption in last 2 weeks	22 ± 11	16 ± 9	7 ± 3	9 ± 3	4 ± 2

cardiogram. Depression of the ST segment was measured during and after peak exercise. A downward-sloping depression of at least 1 mm persisting for 0·08 s or longer in at least 5 consecutive beats was considered indicative of ischaemia.

Results

For brevity we have summarised our results as mean values with the standard error (SE) of the mean. Tables of more detailed data are available from D.J. Statistical analysis is based on the Wilcoxon Signed Rank Sum Test and Student's t test.

(i) ATENOLOL COMPARED WITH PROPRANOLOL

Anginal attack rate and consumption of glyceryl trinitrate

The attack rate and glyceryl trinitrate consumption for each period of treatment are shown in Table 1. Atenolol 25 mg b.i.d. ($P < 0{\cdot}05$), atenolol 50 mg b.i.d. ($P < 0{\cdot}01$), atenolol 100 mg b.i.d. ($P < 0{\cdot}01$), and propranolol ($P < 0{\cdot}01$) significantly reduced anginal attacks when compared with the placebo run-in period. The frequency of anginal attacks was lowest when the two higher doses of atenolol and propranolol were administered. There was no significant difference between the reduction of anginal attack rate achieved by propranolol and any of the three dose levels of atenolol.

Heart rate and blood pressure

Compared with placebo, all treatments significantly reduced heart rate at rest and on exertion ($P < 0{\cdot}001$) and similarly reduced systolic blood pressure ($P < 0{\cdot}001$) (Table 2). There were no significant effects on diastolic blood pressure. Atenolol 100 mg twice daily and propranolol significantly reduced resting and exercise heart rate when compared with atenolol 25 mg twice daily ($P < 0{\cdot}05$). There were no other differences between the active treatment periods.

Exercise tests

The exercise time was prolonged by all active treatments when compared with placebo ($P < 0{\cdot}05$), but there was no difference between the individual randomised double blind active treatment periods. ST depression was significantly reduced by atenolol in doses of 50 mg b.i.d., 100 mg b.i.d. and propranolol when compared with placebo ($P < 0{\cdot}05$). Atenolol 25 mg b.i.d. was significantly less effective in this respect than the higher concentrations of atenolol or propranolol ($P < 0{\cdot}05$).

(ii) ATENOLOL ONCE DAILY COMPARED WITH ATENOLOL TWICE DAILY

The total daily dose of atenolol was 200 mg in 7 patients and 100 mg in 2 patients.

Anginal attack rate and glyceryl trinitrate consumption

The total number of anginal attacks and tablets of glyceryl trinitrate consumed for the last two weeks of each month are shown in Table 3. Both once daily and twice daily atenolol significantly reduced anginal attacks ($P < 0{\cdot}01$) and glyceryl trinitrate consumption ($P < 0{\cdot}01$) when compared with

Table 2 *Mean (± SE of mean) changes in heart rate and blood pressure at rest and on exertion*

		Placebo	*Atenolol* *25 mg twice daily*	*Atenolol* *50 mg twice daily*	*Atenolol* *100 mg twice daily*	*Propranolol* *80 mg thrice daily*
Heart rate/min	At rest	84 ± 5	65 ± 4	62 ± 4	60 ± 4	60 ± 4
	On exertion	145 ± 5	112 ± 4	107 ± 5	101 ± 4	101 ± 2
Systolic blood pressure	At rest	140 ± 5	116 ± 5	114 ± 3	116 ± 5	117 ± 6
	On exertion	166 ± 5	132 ± 7	133 ± 4	133 ± 5	129 ± 5
Diastolic blood pressure	At rest	77 ± 4	74 ± 6	70 ± 3	73 ± 3	73 ± 4
	On exertion	78 ± 6	71 ± 5	76 ± 4	73 ± 3	80 ± 2
Exercise time (s)		104 ± 16	133 ± 24	128 ± 16	135 ± 25	132 ± 16
ST depression on exercise (mm)		1·4 ± 0·48	1·13 ± 0·40	0·57 ± 0·20	0·86 ± 0·21	0·89 ± 0·30

Table 3 *Summary of clinical findings (mean ± SE of mean)*

	Placebo	*Atenolol once daily*	*Atenolol twice daily*
Anginal attacks in last 2 weeks	49 ± 16·6	22 ± 5·9	23 ± 6·2
Glyceryl trinitrate in last 2 weeks	28 ± 17	6·6 ± 2·8	8·4 ± 4·2
Systolic blood pressure (mmHg)	140 ± 5	116 ± 3·5	109 ± 3·1
Diastolic blood pressure (mmHg)	79 ± 3·5	71 ± 2·6	69 ± 2·0
Pulse rate (beats/min)	84 ± 5·4	62 ± 3·2	64 ± 3·8

Table 4 *24-hour ambulatory tape recordings (mean ± SE of mean)*

	Placebo	*Atenolol once daily*	*Atenolol twice daily*
Hourly heart rate (beats)	4505 ± 172	3761 ± 65	3630 ± 101
Maximum heart rate/min	124 ± 7·2	82 ± 6·0	89 ± 5·8
Minimum heart rate/min	63 ± 3·3	53 ± 3·5	53 ± 3·5

placebo. There were no significant differences between once or twice daily atenolol with regard to attack rate but once daily atenolol was slightly more effective in reducing glyceryl trinitrate consumption ($P < 0{\cdot}05$). Seven patients could detect no difference between once daily or twice daily atenolol whereas 2 patients were subjectively worse on the once daily regimen.

Heart rate and blood pressure

When compared with placebo both once daily and twice daily atenolol significantly lowered systolic blood pressure ($P < 0{\cdot}001$) and diastolic blood pressure ($P < 0{\cdot}05$) as well as heart rate ($P < 0{\cdot}001$) (Table 3). There was no significant difference between once or twice daily atenolol.

24-hour ambulatory electrocardiograms

The 24-hour ambulatory tape recordings were analysed to document heart rate by a trained technician who was unaware of which treatment the patient had been taking. The results are presented in Table 4 and show no significant difference on a group basis between once daily or twice daily atenolol. Further, both regimens significantly reduced the mean hourly heart rate for the whole 24 hours when compared with placebo ($P < 0{\cdot}001$) (Fig. 1). All patients were analysed individually as well (Fig. 2) and in 2 instances atenolol once daily produced significantly lower heart rates than twice daily ($P < 0{\cdot}001$ and $P < 0{\cdot}01$). Twenty-one episodes of pain occurred during tape recording. Though pain occurred at the maximal heart rate for the 24-hour period in some cases, in others it did not, and though a given heart rate produced pain in an individual on one occasion, it did not do so on others (Fig. 3).

SIDE EFFECTS AND TOXICITY STUDIES

Twice during the run-in period and at the end of each month of treatment the haemoglobin level,

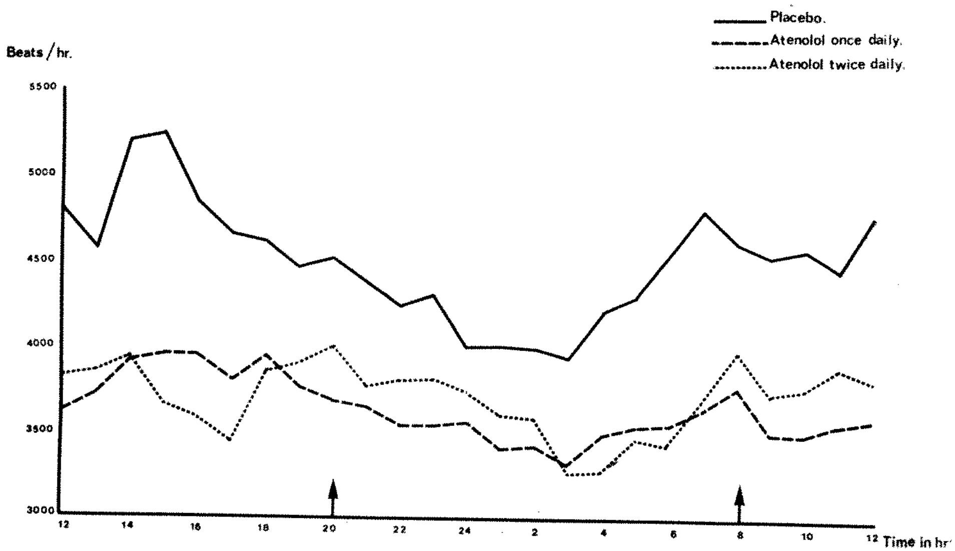

Fig. 1 *Mean hourly heart rate for placebo and atenolol once or twice daily. Arrows indicate time tablets taken.*

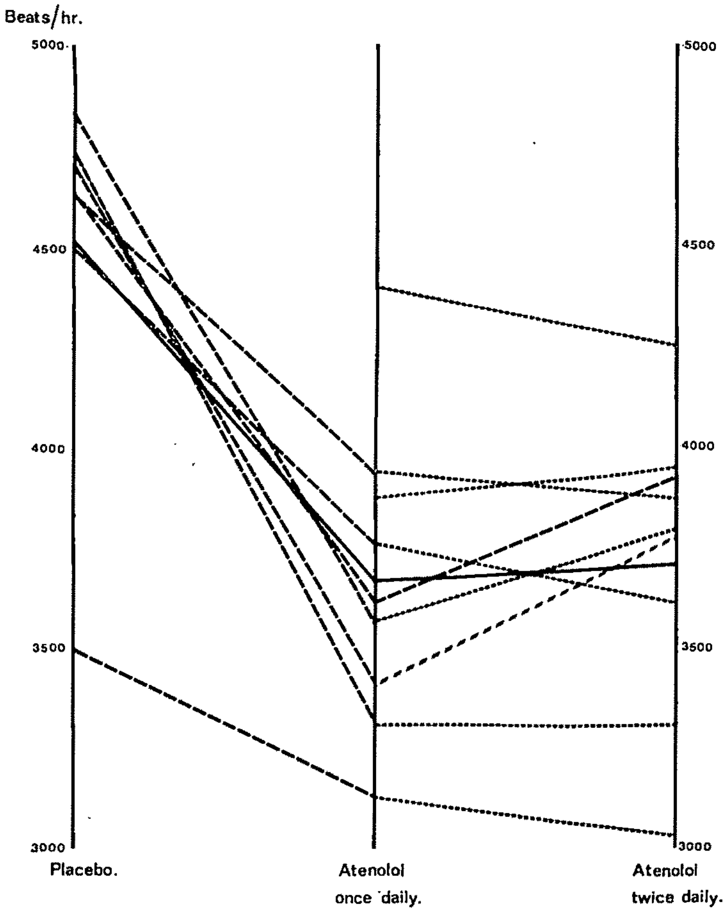

Fig. 2 *Hourly heart rate reduction for individual patients.*

erythrocyte sedimentation rate, results of liver function tests, urea and electrolytes, antinuclear factor titre, and appearances on urine microscopy were recorded. There were minor changes between treatments but none of significance compared with placebo. Twelve side effects were recorded in 5 patients. Headaches and malaise occurred in 2 patients on placebo, 2 on atenolol, and 2 on propranolol. Aching legs occurred in 2 patients on atenolol 50 mg twice daily, 1 on atenolol 25 mg twice daily, and 2 on propranolol. All were tolerated and were only mentioned after direct questioning.

Discussion

The best means of assessing the degree of beta-blockade and in turn the potency and effectiveness of any new agent is by dose titrating the drug under study until there is optimum peak exercise heart rate reduction (Jackson *et al.*, 1975b). Once this has been established a double-blind comparison with propranolol, the standard reference agent, is essential.

In this study, we have compared a dose titration of atenolol in a double blind randomised fashion with 80 mg thrice daily propranolol, which is generally held to be an effective dose (Jackson *et al.*, 1975a). The initial design of this study included a randomised double blind placebo period. However, the possibility of exaggeration of angina or precipitation of myocardial infarction after sudden withdrawal of beta-blockade now makes this type of trial unethical (Diaz *et al.*, 1973; Nellen, 1973; Slome, 1973; Alderman *et al.*, 1974; Miller *et al.*, 1975). Consequently, in our study all active agents were compared with each other and with the single blind placebo run-in period.

In comparing atenolol with propranolol all active agents significantly reduced the anginal attack rate and glyceryl trinitrate consumption. The two higher

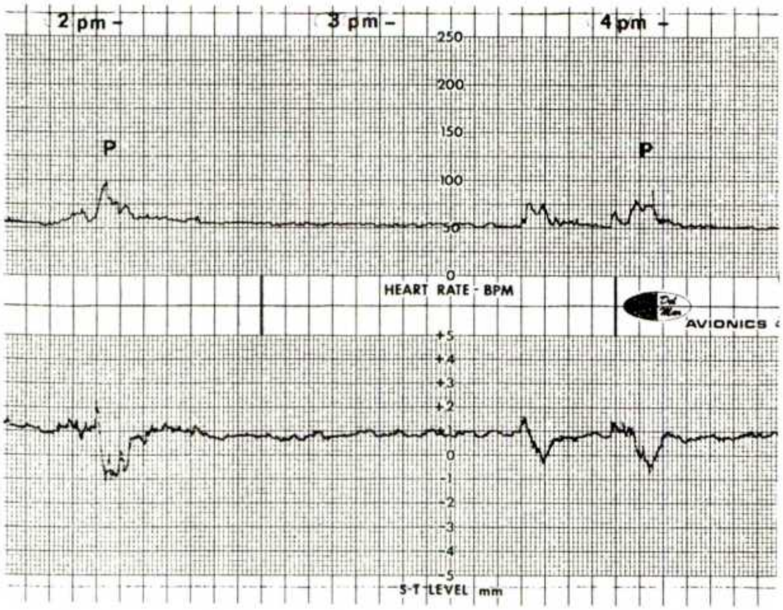

Fig. 3 *Heart rate and ST segment trend recording. Pain occurred with an increase in heart rate on 2 occasions (P) but not with a similar increase on another. ST segment depression is clearly shown.*

doses of atenolol and propranolol were more effective than atenolol 25 mg twice daily.

Adrenergic beta-receptor antagonists reduce myocardial oxygen consumption mainly by reducing heart rate and systolic blood pressure (Balcon, 1971). All active agents significantly ($P < 0{\cdot}001$) reduced resting and exercise heart rate and systolic blood pressure. Atenolol 100 mg twice daily produced a similar peak exercise heart rate reduction to propranolol 80 mg thrice daily and the two are probably equipotent in man. In addition, all drugs significantly prolonged exercise time to pain when compared with single blind placebo ($P < 0{\cdot}05$) but no differences emerged between active agents.

Our results, therefore, show that the beta-adrenoceptor blocking drug atenolol, in optimal dosage, is as effective as propranolol in reducing the attack rates and glyceryl trinitrate consumption in patients with angina pectoris. Further, the results show that there is no difference in these subjective measurements between atenolol given as a single daily dose or as a twice daily dose. The collection of subjective data is, however, dependent upon patients accurately recording attacks, etc. on their record cards for subsequent analysis, and, as such, even with good motivation on the part of the patient, must be subject to some error (Lawrie *et al.*, 1976). Usually an exercise tolerance test of some kind is carried out during each treatment period in an attempt to obtain an objective assessment of the drugs' antianginal activity. However, this suffers from the disadvantages of being carried out in an artificial hospital setting, of recording only one small time period to represent the whole of the treatment period (usually one month), and of being an artificial form of exercise (Jackson *et al.*, 1975b).

We have attempted to overcome the problem of the hospital exercise test by obtaining an objective assessment of the heart rates from a group of patients during their normal daily lives. This has been made possible by the use of 24-hour ambulatory tape recordings of heart rate during treatment with placebo and active agents. The aim of this monitoring was to determine if patients have episodic heart rate increases, that is, sympathetic nerve activity and/or vagal withdrawal which may be related to anginal attacks, and if the heart rates are more stable when the patients are taking beta-blocking drugs. The results showed that atenolol, whether given once daily or twice daily, did reduce the overall hourly heart rate and that the mean maximum heart rate achieved during the 24-hour recording for the group was indeed lower than when the patients were on placebo (124 beats/min on placebo, 83 beats/min on atenolol once daily, and 89 beats/min on atenolol twice daily). If it is accepted that the heart rate reduction is important in achieving beneficial response when beta-blocking drugs are used to treat angina pectoris (Jackson *et al.*, 1975b), then this was achieved with atenolol. We feel that this type of objective ambulatory electrocardiographic recording is an important requirement in the assessment of beta-blocking drug therapy, particularly when an agent under study is being administered only once per 24 hours.

Thus our study shows that atenolol is effective as an antianginal agent given once a day. However, 2 patients found on the once a day therapy that their symptoms were worse in the evenings. It is interesting to note that in contrast to the other 7 patients, these 2 worked hardest in the evening rather than during the day (one was a publican and the other a part-time mechanic). With these 2 patients in mind, we believe these results show that atenolol 100 mg can be initially prescribed once a day for patients with angina pectoris, perhaps increasing to 200 mg/day to obtain maximum benefit; occasionally patients may benefit from an additional dose in the evening. We believe this drug offers practical advantages to the working patient.

We are grateful for the help of Frances Weaver, Lindsay Kitson, and Anne Evans with the tape recordings.

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Cardiac effects of tricyclic antidepressant medication
A preliminary study of nortriptyline

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SUMMARY Systolic time intervals and drug plasma concentrations have been measured in a group of patients receiving repeated treatment with nortriptyline. Significant positive correlations between plasma nortriptyline levels and prolongation of pre-ejection phase ($P < 0{\cdot}005$) and increase in the ratio pre-ejection phase, left ventricular ejection time ($P < 0{\cdot}05$) were obtained. A deterioration in cardiac function, with increase in heart rate, resulting in a negative inotropic effect has been shown to occur with therapeutic doses of nortriptyline. The potential dangers of tricyclic antidepressant drugs on the heart in patients whose myocardium is already compromised or those who accumulate high plasma concentrations are emphasised.

During the past two decades the tricyclic antidepressant group of drugs has become firmly established as an effective treatment for various types of depressive illness. However, in this same period there have appeared numerous reports of cardiovascular complications following overdosage with this group of drugs (Barnes *et al.*, 1968; Sacks *et al.*, 1968; Crocker and Morton, 1969; Freeman *et al.*, 1969; Noble and Matthew, 1969; Brown *et al.*, 1971; Ruddy *et al.*, 1972; Sedal *et al.*, 1972; Brown *et al.*, 1973; Roberts *et al.*, 1973).

These complications have included sinus or supraventricular tachycardia, widening of the QRS complex, ST depression, bundle-branch block, hypotension, myocardial infarction, and heart block. Of more serious consequence, many of these changes have been observed in patients receiving only therapeutic doses of tricyclic drugs (Stoman, 1960; Kristiansen, 1961; Alexander and Niño, 1969; Williams and Sherter, 1971; Scollins *et al.*, 1972). Moreover, there have also been reports of an increased incidence of sudden death in elderly patients as a result of treatment with this group of drugs (Coull *et al.*, 1970; Moir *et al.*, 1972). In a number of these 'tricyclic deaths' necropsy has shown similar focal myocardial necrosis to that found in animals receiving prolonged noradrenaline infusions (Wexler *et al.*, 1967), or in humans with phaeochromocytoma (Northfield, 1967).

However, the majority of these early studies have concerned single case reports; very few controlled investigations have been carried out until recently.

In a study by Freyschuss *et al.* (1970), the effect of nortriptyline medication on various cardiovascular parameters was investigated in a group of 40 depressed patients. These workers reported that, apart from a general increase in heart rate, in all but one patient the electrocardiogram both at rest and during exercise showed no abnormal changes during nortriptyline medication. However, there was one patient with a very high plasma nortriptyline level who produced a right bundle-branch block during an exercise test. A similar study was later carried out by Vohra *et al.* (1975), who investigated the electrocardiograms of a group of 32 depressed patients who were being treated with various tricyclic antidepressant drugs. In these patients a moderate increase in heart rate and a small prolongation of the PR interval was demonstrated.

In contrast to these earlier findings, Burrows *et al.* (1974) reported significant effect on atrioventricular conduction during therapeutic medication with nortriptyline, though His bundle electrography was used to obtain these findings. Further, in a case reported by Kantor *et al.* (1975), a 2:1 atrioventricular block developed in an elderly patient during treatment with imipramine which was directly related to the drug-plasma concentration, the block occurring below the atrioventricular node in the His-Purkinje system.

Using a somewhat different approach, Müller and Burckhardt (1974) investigated the effect of various tri- and tetracyclic antidepressants on cardiac function using the technique of systolic time interval

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changes (STI). The results of these studies were interpreted by the authors as evidence of a reduced myocardial contractility during prolonged treatment with these drugs.

It has been shown by many workers that the measurement of systolic time intervals is a reliable, repeatable, and simple noninvasive method of assessing myocardial performance; more specifically, the technique measures the contractile state of the left ventricular myocardium (Spodick and Kumar, 1968; Weissler *et al.*, 1968; Martin *et al.*, 1971; Carliner *et al.*, 1974; Frei *et al.*, 1974). This present study is a preliminary investigation into the effects of repeated therapeutic doses of nortriptyline upon myocardial function in a small group of patients using the techniques of STI measurement, with the simultaneous determination of plasma nortriptyline concentrations.

Patients and methods

MEASUREMENT OF STI CHANGES

The STI values are obtained from a simultaneous fast speed recording of the electrocardiogram, phonocardiogram, and the carotid wave form. The total electromechanical ejection time (QS_2) is measured from the start of the QRS complex in the electrocardiogram to the first high-frequency vibrations of the second heart sound. Left ventricular ejection (LVET) is measured from the beginning upswing to the base of the incisural trough of the carotid arterial pulse tracing. Pre-ejection phase (PEP) is obtained by subtracting the left ventricular ejection time from the total electromechanical systole ($QS_2 - LVET$).

The STI values obtained vary with individual heart rates in a linear manner and previously published regression relations for the normal resting supine subject were used to calculate a further index PEPc (Weissler *et al.*, 1968). Deviation from normal (expected) values of this function were calculated as the difference between observed intervals (PEP) and those predicted from the normal regression line (PEPc). The recordings of STIs for the present studies were made using a Cambridge multichannel recorder and Statham gold cell displacement transducer. These recordings were obtained at a chart speed of 100 mm/s, at which the measurements were judged accurate to 5 ms. Recordings were taken with the subjects in a resting state, supine, with the trunk, head, and neck raised to 30°, during an arrested expiration. Measurements were made over three cycles, with the final results expressed as the mean.

Table *Age, sex, weight, diagnosis, and dose of nortriptyline for patients in study*

Case No.	*Age (y)*	*Sex*	*Weight (kg)*	*Maximum dose of nortriptyline (mg 1 day)*	*Clinical diagnosis*
1	54	M	66	150	Obstructive airways disease and mild depression
2	52	M	70	150	Mild depression
3	53	M	70	150	Mild depression
4	36	F	58	50	Mild depression
5	36	F	58	150	Mild depression
6	22	F	47	150	Anorexia nervosa and mild depression
7	71	M	64	150	Mild depression
8	44	M	89	150	Mild depression

PATIENTS

Eight patients who presented with various psychosomatic complaints were the subjects of the study. The age, sex, weight, and clinical diagnosis of these patients are shown in the Table. Before inclusion into the study patients were fully examined clinically and with chest *x*-rays and resting and exercise electrocardiograms before being judged free of cardiac disease.

After obtaining baseline (drug-free) measurements of the STIs for each subject, gradually increasing therapeutic doses of nortriptyline were prescribed over several weeks, with a period of at least 7 days on each dosage schedule; each patient acted as his or her own control. Further measurements were taken from each subject on a number of occasions during the nortriptyline treatment period, these being obtained at the same time of day on each occasion. No concomitant treatment was allowed for any patient during the study, so that the effects of barbiturates on the metabolism of nortriptyline could be avoided, and the patients were asked to abstain from alcohol during this period (Zirkle *et al.*, 1959). No patient during the trial period developed any alteration of intraventricular conduction. Finally, measurements were taken one week after the cessation of nortriptyline in order to obtain a second baseline result.

PLASMA NORTRIPTYLINE CONCENTRATIONS

Heparinised venous blood samples were obtained from each subject at the same time as the measurement of STI values. The blood was centrifuged at 3000 rpm and the plasma removed and stored in fresh plastic tubes at −20°C before analysis. The estimation of plasma nortriptyline concentration was carried out in duplicate using a modification of the gas chromatographic technique of Braithwaite and Widdop (1971). The method had a lower limit

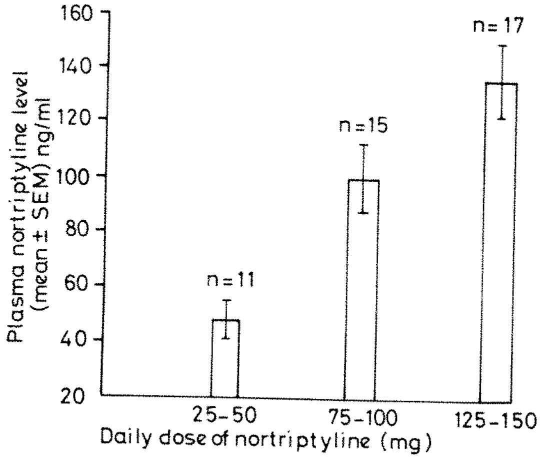

Fig. 1 *Relation between daily dose and mean plasma nortriptyline levels.*

of sensitivity of 20 ng/ml and the agreement between duplicate estimations was within 10 per cent.

Results

The relation between the daily dose of nortriptyline and mean steady-state plasma nortriptyline levels obtained in the 8 patients investigated is shown in Fig. 1, which shows that increased doses of nortriptyline produced expected rises in steady-state plasma nortriptyline levels. These results indicate that patients were obtaining therapeutic plasma nortriptyline concentrations during the trial.

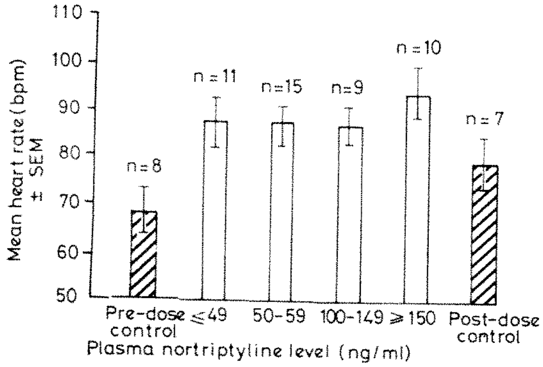

Fig. 2 *Relation between mean heart rate and plasma nortriptyline levels.*

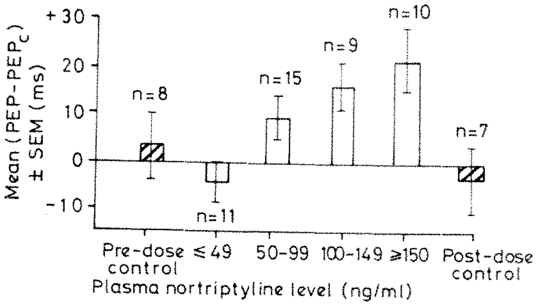

Fig. 3 *Relation between difference in observed pre-ejection phase (PEP) and normal calculated value (PEPc) and plasma nortriptyline level.*

HEART RATE (HR)

Fig. 2 shows the relation between mean heart rate and plasma nortriptyline concentrations. It can be seen that the increase in heart rate obtained during nortriptyline medication appears not to rise with increasing drug plasma concentrations. The increase in heart rate during medication was reversible upon stopping the drug and post-dosage mean heart rate was similar to that obtained before treatment.

PRE-EJECTION PHASE (PEP-PEPC)

Fig. 3 shows the relation between the difference between observed (PEP) and predicted values (PEPc) with increasing plasma nortriptyline concentration. As can be seen from this figure, there seems to be a positive relation between deviation from normal values (that is, increase in PEP disproportionate to PEPc) and increasing antidepressant concentrations. Moreover, a linear regression analysis of change in pre-ejection phase values, Δ (PEP-PEPc), against plasma nortriptyline levels for all the observations produced a statistically significant correlation ($r = +0{\cdot}42$, $n = 44$, $P < 0{\cdot}005$). Fig. 3 also shows that post-dosage PEP values returned to those obtained before dosing and the effect of nortriptyline treatment on pre-ejection phase values was reversible.

RATIO PEP/LVET

Fig. 4 shows the relation between the ratio of PEP/LVET and plasma nortriptyline concentrations. As can be seen from this figure, there appears to be a clear increase in this ratio with increasing antidepressant concentrations. A linear regression analysis of change in ratio $\left(\Delta \frac{\text{PEP}}{\text{LVET}}\right)$ against plasma nortriptyline concentrations for all observa-

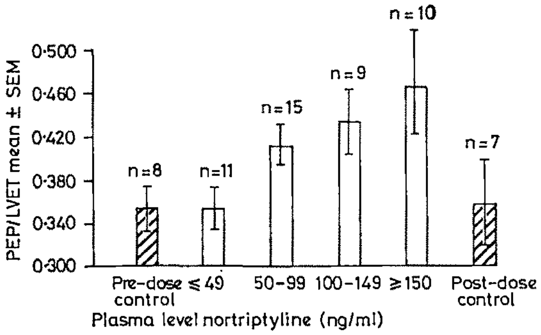

Fig. 4 *Relation between ratio of pre-ejection phase (PEP) to left ventricular ejection time (LVET) and plasma nortriptyline level.*

tions produced a statistically significant correlation ($r = +0{\cdot}32, n = 45, P < 0{\cdot}05$). Fig. 4 also shows that post-dosage values returned to those obtained before dosage.

Discussion

In the present investigation of the effect of therapeutic plasma nortriptyline concentrations on systolic time intervals, measured in a small group of patients without signs of cardiac disease, significant increases in heart rate accompanied by an elongation in PEP interval and an increase in the ratio $\frac{\text{PEP}}{\text{LVET}}$ have been found. The increases in PEP and $\frac{\text{PEP}}{\text{LVET}}$ ratio were both found to be greatest at highest plasma nortriptyline concentrations. These findings, therefore, seem to be consistent with those of Müller and Burckhardt (1974) where similar changes in STI were observed for several other tricyclic antidepressants including amitriptyline, though plasma concentrations were not measured.

The increase in heart rate produced by nortriptyline was immediate and did not appear to be influenced either by dosage or plasma nortriptyline concentration and was reversible on cessation of dosage. This chronotropic effect of nortriptyline, unrelated to drug plasma concentration, is in agreement with the findings of Freyschuss *et al.* (1970) and may be a result of the drug's anticholinergic action on the vagus.

Nortriptyline, as with other similar tricyclic antidepressants, is a potent inhibitor of the re-uptake process for noradrenaline at the presynaptic site of the adrenergic neurone, and the magnitude of this primary effect appears to be related to the plasma nortriptyline concentration (Åsberg, 1974). Thus, the relation between increase in systolic time intervals $\left(\text{PEP and } \frac{\text{PEP}}{\text{LVET}}\right)$ and plasma nortriptyline concentration obtained in the present study is evidence that the drug has a direct effect on the myocardium, the mechanism of which may be related to the drug's interaction with adrenergic nerve function. The findings of Burrows *et al.* (1974) that atrioventricular conduction was prolonged by more than 30 ms in patients with plasma nortriptyline levels above 200 ng/ml seem to be consistent with our own findings. Further, it has been reported by Åsberg (1974) that potentially dangerous side-effects of nortriptyline medication such as electrocardiographic disturbances and 'sudden falls' have always occurred on high plasma nortriptyline concentrations.

A majority of studies have now shown that high steady-state plasma nortriptyline concentrations are associated with a poor therapeutic outcome, with optimum response being obtained within an 'intermediate' plasma level range (Åsberg *et al.*, 1971; Kragh-Sørensen *et al.*, 1973, 1976; Ziegler *et al.*, 1976; Montgomery *et al.*, 1977). A therapeutic range of 50 to 150 ng/ml is now recommended for treatment with nortriptyline (Kragh-Sørensen *et al.*, 1976). Large differences in steady-state plasma levels are routinely observed in individual patients receiving antidepressant therapy with nortriptyline, with some patients accumulating extremely high levels (Montgomery *et al.*, 1977). The occurrence of these high, and therapeutically ineffective, nortriptyline concentrations on relatively small doses is the result of a slow hepatic clearance of the drug in some patients (Braithwaite *et al.*, 1978).

The cardiac dangers associated with tricyclic antidepressant medication seem to be very real, particularly in those patients who accumulate very high plasma antidepressant concentrations, for example the elderly or those patients with impaired hepatic function. High plasma levels are also unnecessary as they now appear to produce a poorer antidepressant effect.

The present findings are of particular clinical interest. The persistent tachycardia and deterioration in inotropic state that might occur during tricyclic antidepressant treatment have a potential danger in those patients whose myocardium is already compromised. Further, the alteration in autonomic balance may be of special importance in those patients with ischaemic heart disease and may account for the episodes of sudden death reported (Coull *et al.*, 1970; Moir *et al.*, 1972).

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Application of an improved intracardiac fibreoptic system

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SUMMARY An improved fibreoptic *in vivo* haemoreflection system has been used in over 200 patients. Continuous recording of oxygen saturation while moving the catheter permits measurement of simultaneous pressure and oxygen saturation at almost an unlimited number of sites through the right heart. The oxygen saturation can be continuously monitored and the response is sufficiently fast to permit investigation of changes in oxygen saturation during portions of the cardiac cycle.

Dye dilution curves have been recorded from over 200 patients. The only blood withdrawn for the dye dilution curve was the 3 ml needed for checking the calibration of the instrument. We have found that the calibration is extremely stable. In some instances where it has been deemed impractical to obtain blood for calibration, the calibration factor for each catheter may be used. In any case, the calibration check is performed at the end of the study and does not present problems of sterility. The calibration factor may yield a correction factor which then applies uniformly to all the cardiac output values obtained during the study.

The development of the fibreoptic technique, which allows continuous measurement of oxygen saturation without withdrawal of blood samples, was a major advance in cardiac catheterisation techniques. The same catheter and instrument may be used to record dye dilution curves for determination of cardiac output or an estimation of the degree of shunts. Practical instruments for such uses were described as early as 1964 by Ensin *et al.*, and in 1965 by Gamble *et al.*, Hugenholtz *et al.*, and Frommer *et al.*

Since the studies noted above, the instruments have been improved by three major changes. (a) Solid state construction, in particular use of light-emitting diodes instead of incandescent lamps and colour filters, has greatly increased the stability and reproducibility of the reading and, at the same time, reduced the bulk and cost of the device. (b) Substitution of the glass optical fibres with plastic ones, which are practically unbreakable, has greatly increased the life and reduced the cost of the catheters. (c) Factory calibration of catheters for both O_2 saturation and dye (indocyanine green) concentration.

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Subjects and methods

Studies were carried on in the cardiopulmonary laboratory, the Children's Medical and Surgical Center of the Johns Hopkins Hospital, and in the Cardiovascular Laboratory at the University of Virginia Hospital. In over 200 children undergoing cardiac catheterisation for a variety of cardiac lesions, studies were carried out with the fibreoptic haemoreflection technique[1] in addition to conventional procedures necessary to establish a diagnosis. In 30 patients, oxygen saturations were determined by means of the fibreoptic technique. In all of these, intracardiac oxygen saturation was measured *in vivo* simultaneously with a sampling of blood through a lumen in the fibreoptic catheter. These samples were analysed by a spectrophotometric method. A diagram of the instrument employed is shown in Fig. 1; the response time can be set in discrete steps between 0·1 and 2 s. Its principle of operation and its construction have been described previously by Polanyi (1974, 1975), and only a brief summary will be given here.

The fibreoptics catheter (Fig. 2) contains a

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[1] Instrument loaned by American Optical Co, Boston, MA.

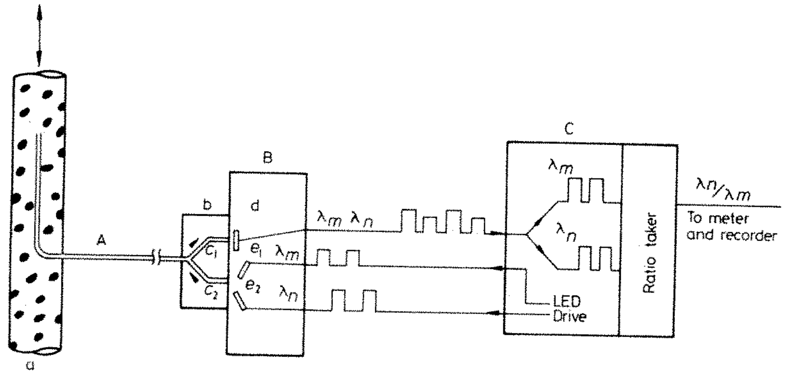

Fig. 1 *Block diagram of* in vivo *oximeter. A—catheter; B—optical box; C—electronic package; a—blood vessel; b—terminal block of catheter; c_1 and c_2—afferent and efferent fibres; d—photocell; e_1 and e_2—light emitting diodes (LED's). (Published through the courtesy of Butterworths, London.)*

number of afferent and efferent optical fibres (1 or 2 of each; 0·25 mm in diameter). The afferent fibres are illuminated in rapid sequence (about 300 cycles per second) by light of two colours from pulsed light emitting diodes. A portion of the light back scattered by the blood cells in the proximity of the tip of the catheter is picked up by the efferent fibres and detected. The ratio of the back scattered light intensities after appropriate scaling is a direct measure of the O_2 saturation, or of dye[2] concentration. The colours of lights (wave length) used in these determinations are centred around 660 nm and 805 nm for O_2 saturation, and around 805 nm and 930 nm for dye concentration. The ratios of the back scattered intensities are taken as 805 nm/660 nm (O_2 saturation) and 930 nm/805 nm (dye concentration).

The catheters used in this study ranged in size from 5F to 7F. The 6F and 7F catheters are equipped with a small lumen (Fig. 2) for sampling and pressure measurements. The catheters are constructed from standard Lehman catheters (Ensin *et al.*, 1964; Gamble *et al.*, 1965).

A smaller catheter 8 cm long and of such size as to pass through a No. 18 gauge Teflon needle,[3] has also been found useful; these catheters are 2 mm longer than the Teflon sheath. They are particularly useful for dye-dilution studies for which only an interarterial needle is used.

CALIBRATION

The catheters are factory calibrated for both dye concentration and oxygen saturation. For O_2 saturation two numbers are supplied: 'gain' and 'standardisation'. After the 'gain' is set, the 'stan-

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[2] Cardio Green.

[3] B-D 'Longdwell' catheter needles by Becton and Dickinson, Rutherford, New Jersey.

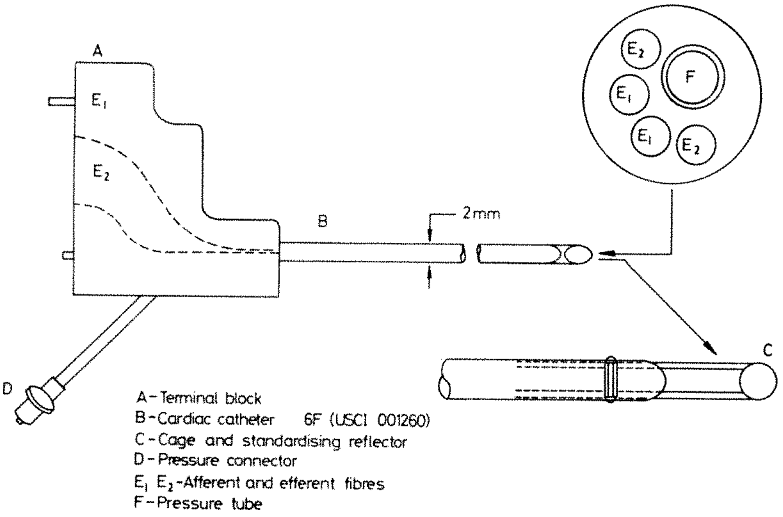
A
E_1
E_2
B
2mm
C
D
E_2
E_1
F
E_1
E_2
A-Terminal block
B-Cardiac catheter 6F (USCI 001260)
C-Cage and standardising reflector
D-Pressure connector
E_1 E_2-Afferent and efferent fibres
F-Pressure tube

Fig. 2 *Schematic drawing of fibreoptics catheter. (Published through the courtesy of Butterworths, London.)*

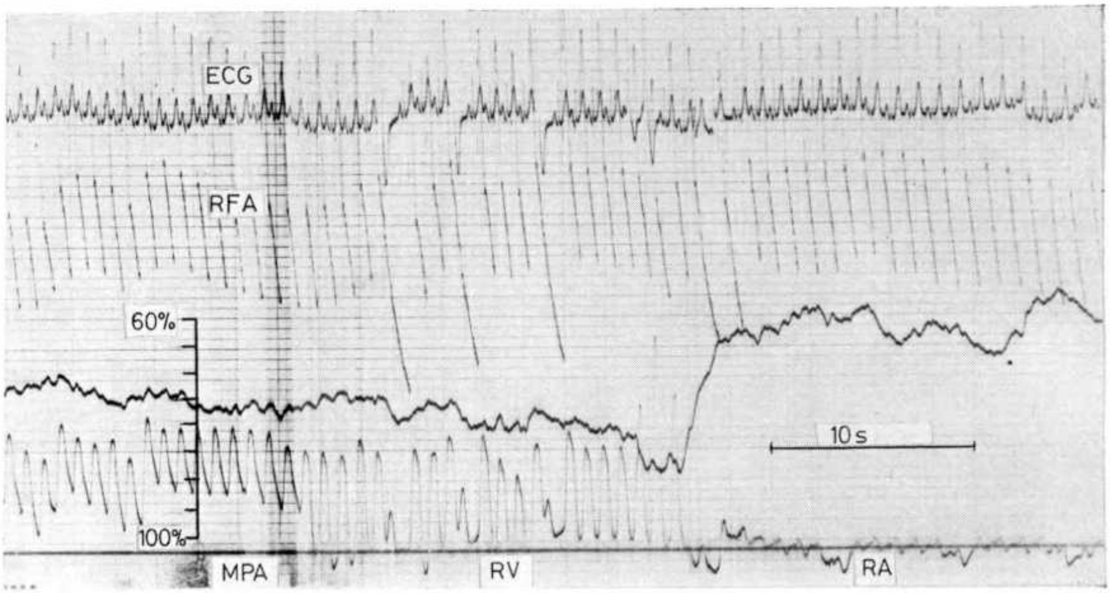

Fig. 3 *Tracings recorded on withdrawal from right pulmonary artery to right atrium in a patient with a ventricular septal defect.*

dardisation' is adjusted with the catheter tip immersed in sterile normal saline. The catheter is then calibrated and ready for use. For dye concentration only the 'gain' factor is needed. Gain may be set at any time during the procedure with the catheter tip *in situ*, before injection of the dye. For cardiac output, the amount of the dye injected is set by discrete steps with a control on the cardiac output computer. The linear range of the system is 0 to 40 mg/litre.

Errors in dye calibration can be caused by (a) differences in the 'strength' of the dye used in the factory calibration and in the procedure, and (b) by variation of the cardiogreen concentration in the injectate caused by dilution errors. A rapid and simple check can be performed at the end of the study using 3 ml of the patient's blood and 50 μl of the dye solution used. Such a check yields, as a rule, a small correction factor to be applied to cardiac outputs obtained with a given dye sample. The 'strength' of the dye itself has been found remarkably uniform from batch to batch.

Results

As a rule, the life of these catheters is limited by the life of the sheath. Factory supplied calibration factors have been found not to vary as long as the catheter is usable. Some of the catheters have been used for as many as 20 cardiac catheterisations.

Clotting has not been a problem with any of these

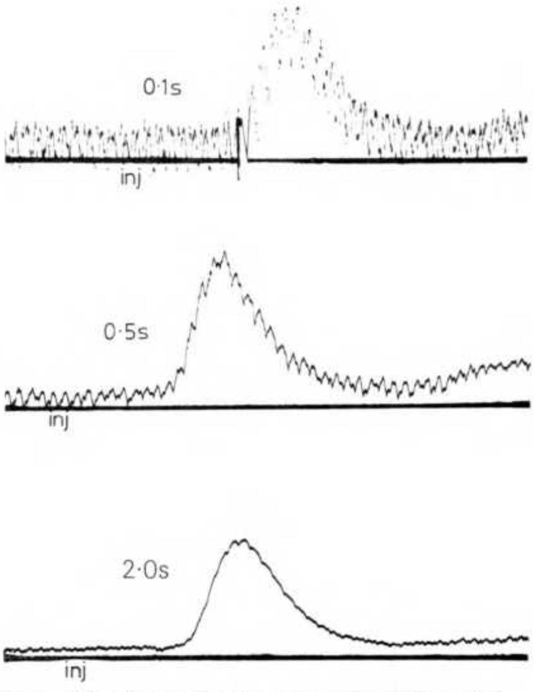

Fig. 4 *The effect of altering response time is illustrated by these dye curves which were done in rapid succession in the same patient. Response time is controlled by the electronics rather than being dependent on dead space volume and the speed of withdrawal of blood, as is the case in the usual dye dilution technique.*

catheters. Our patients are routinely heparinised with 1000 units heparin/kg before the introduction of arterial catheters. We have not noticed any deposition of fibrin of sufficient magnitude to alter the oximetry measurements or to be detectable visually.

Fig. 3 shows a typical tracing of a pullback in a patient with a ventricular septal defect. Continuous arterial oxygen saturation readings were obtained upon withdrawal from the right pulmonary artery to the right atrium in a patient with a small left-to-right shunt.

Fig. 4 shows a set of typical indicator dilution curves in a patient with no shunt. The effect of varying the response time is obvious. For dye curves where only the cardiac output is of interest the 2·0 second response time is best.

Discussion

Since the initial introduction of the fibreoptic techniques in 1962, acceptance of the instrument has been slow. This has been caused in part by the spurious readings obtained when the tip of the catheter is in close proximity to or in actual contact with cardiovascular endothelium. Another problem has been the expense of the basic instrument and of the catheters. It was found that glass bundles were subject to breakage and were often unusable after as few as three or four studies.

The present instrument seems to be vastly superior to earlier models. It is equally rapidly responding and is particularly useful for indicator dye dilution techniques. It was found to be capable of detecting small left-to-right shunts and in some instances capable of localising the ventricular septal defects in the outflow portion of the ventricle, clearly indicating the difference in location of the shunt as opposed to a muscular defect.

The instrument is particularly useful for dye dilution techniques since one does not need to withdraw blood through a densitometer. Withdrawal of blood through a densitometer means that one must take care to maintain sterility and to avoid the introduction of air bubbles into the patient. For larger size patients the blood is often discarded but this is obviously impractical for small infants and children. In addition, the response time of the densitometer depends directly upon flow rate through the densitometer as well as inversely upon dead space. It is impractical for the dead space to be less than 0·3 ml and it is difficult to achieve flow rates much greater than 30 to 40 ml per second Furthermore, flow rates as low as 15 ml per second. have been shown to alter the haemodynamics of neonates during the withdrawal (Gessner *et al.*, 1965).

The fibreoptic system requires no withdrawal of blood and thus simplifies the problems of sterile technique. It also avoids completely the need for withdrawal and reinfusion with all its incumbent hazards of air embolism. In addition, response time can be controlled by the electronics rather than being dependent upon the dead space or the withdrawal rate. Since there is no necessity to reinfuse blood, the next indicator dilution curve may be run as soon as baseline stability is reached, usually within 30 seconds. In practice, this means that dye curves and cardiac outputs may be obtained at very brief intervals to check upon changing haemodynamics during drug infusion or similar dynamic studies.

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Right ventricular monophasic action potentials in patients with long QT syndrome

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SUMMARY In 3 patients with the long QT syndrome, one caused by quinidine and 2 of congenital origin, right ventricular monophasic action potentials were excessively prolonged and of varying shapes in different recording sites. In addition, effective refractory periods of the ventricular muscle were abnormally long.

The prolongation of the QT interval associated with syncopal attacks can be encountered in two different situations: the long QT syndrome of congenital origin (Jervell and Lange-Nielsen, 1957; Romano *et al.*, 1963; Ward, 1964; Phillips and Ichinose, 1970) and the acquired form (Motté *et al.*, 1970; Reynolds and Vander Ark, 1976). The latter may be found in association with various conditions such as atrioventricular block, sinus bradycardia, or the use of drugs of which quinidine, phenothiazines, and amiodarone are examples. Though a totally different pathogenic mechanism was suggested for these two syndromes, the common clinical and electrocardiographic features must have a common electrophysiological basis.

In this paper we present our findings in 3 patients with this syndrome in whom monophasic action potentials were recorded from the right ventricle.

Methods

The technique for recording monophasic action potentials was presented in a former paper (Gavrilescu *et al.*, 1972). Close bipolar suction electrodes were passed percutaneously and positioned in the right ventricle. Applying gentle pressure an injury current was obtained. Suction applied with a simple device fixed the electrode in the chosen position and made possible the recording of the monophasic action potential. The negative pressure within the suction system was about 46·5 kPa; it was applied for periods of 2 minutes in order to avoid endocardial lesions. Only stable tracings with an amplitude exceeding 25 mV, and not distorted by artefacts, were analysed. The recordings were obtained from lateral wall, base, septal wall, and apex of the right ventricle. Monophasic action potential duration was measured at 90 per cent of repolarisation. The refractory period of the right ventricular myocardium was determined using the extra-stimulus method (Wit *et al.*, 1970) and was synchronised with the monophasic action potential recordings. The stimulus strength of the test impulse was twice the diastolic threshold. Both monophasic action potential recordings and refractory period determination were performed at various cycle lengths.

Subjects

CASE 1

A 49-year-old woman with mitral valvular disease and atrial fibrillation was converted to sinus rhythm by DC shock. In the next few hours she developed syncopal attacks, after 1 g quinidine sulphate (Fig. 1B). A prolonged QT interval was noted immediately after the cessation of ventricular tachycardia (Fig. 1A and B). Monophasic action potential recordings (Fig. 2) were then obtained. There were no electrolyte disturbances, and the QT interval returned to normal values after 72 hours (Fig. 1C).

CASE 2

A previously healthy 32-year-old woman was referred to us for cardiac evaluation following an episode of syncope caused by ventricular fibrillation. Frequent multiform ventricular beats, a prolonged QT interval, and alternation of the T wave had been noted after her resuscitation (Fig. 3A and B). On admission there were no abnormal findings with the exception of the long QT interval and inverted T waves (Fig. 3A). She had normal hearing. The electrophysiological study was performed and monophasic action potentials recorded at different sites in the right ventricle showed varying durations and shapes (Fig. 4).

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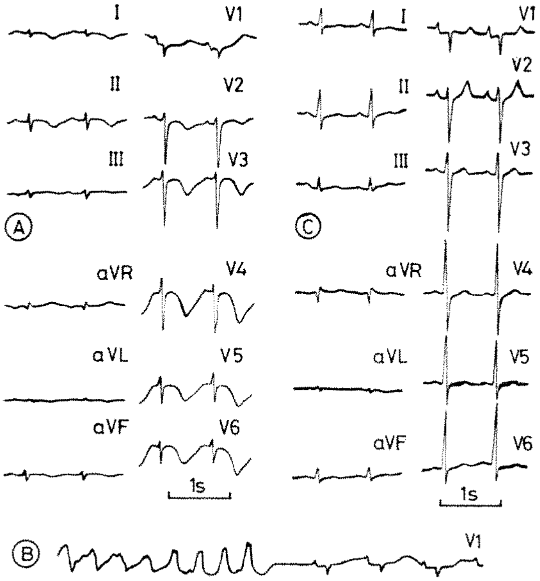

Fig. 1 *Case 1. Surface electrocardiogram showing: (A) long QT interval and bizarre T and U waves, quinidine induced; (B) ventricular tachycardia during syncopal attacks; and (C) reversion to normal QT interval after drug withdrawal.*

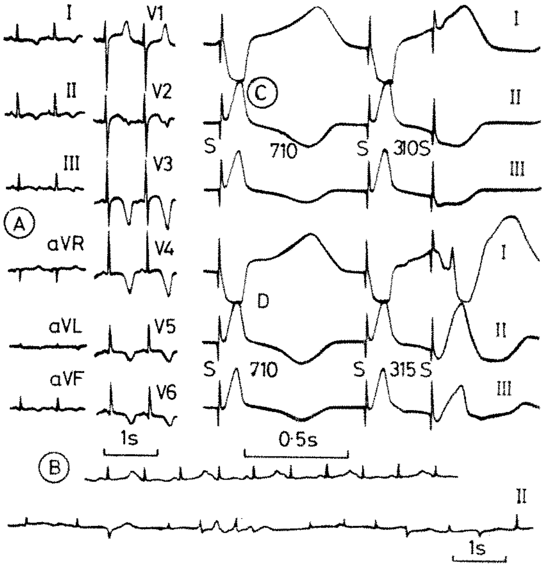

Fig. 3 *Case 2. Surface electrocardiogram at admission (A), with T + U wave alternans and multiform ventricular ectopic beats (B), and the determination of the refractory period of the right ventricle. (C) effective refractory period, 310 ms; (D) functional refractory period, 315 ms.*

CASE 3

This case has been reported elsewhere (Gavrilescu and Luca, 1976). A 17-year-old boy had repeated attacks of ventricular tachycardia, the arrhythmia being interpreted as caused by re-entry within the bundle-branches. At the cessation of some of the arrhythmic episodes he showed a prolonged QT interval and inverted T waves. Electrophysiological study was performed during such a period and the tracings were similar to those obtained in case 2 (Fig. 5). Monophasic action potential recordings from the apex and septal wall of the right ventricle showed a second deflection (Fig. 5C), which became more apparent at a faster driving rate (Fig. 5D).

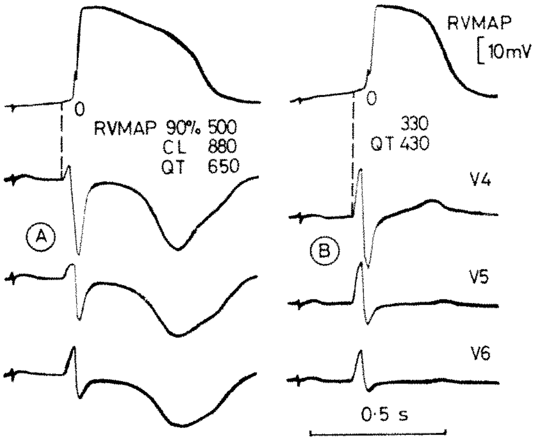

Fig. 2 *Case 1. Right ventricular monophasic action potential recording (RV MAP): (A) during prolonged QT interval, and (B) after reversion to normal. CL, cycle length.*

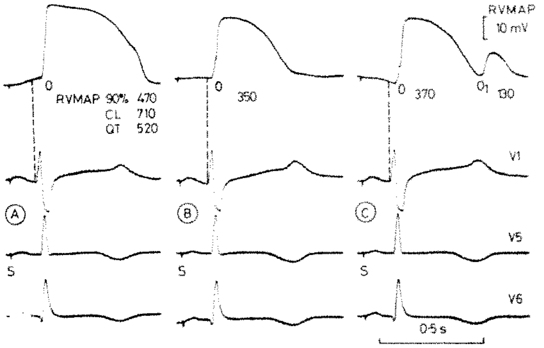

Fig. 4 *Case 2. Right ventricular monophasic action potential recordings (RV MAP) from: (A) lateral wall, (B) base, and (C) apex and septal wall.*

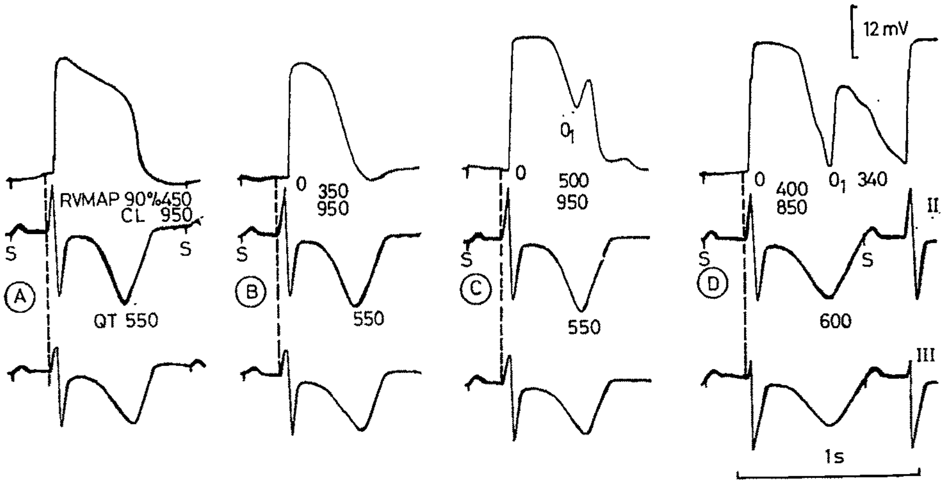

Fig. 5 *Case 3. Right ventricular monophasic action potential recordings (RV MAP) from: (A) lateral wall, (B) base, (C) apex and septal wall, and (D) during pacing at a faster rate (CL = 850 ms). In D the second monophasic action potential deflection (0_1) was detached and became more apparent. (For more details see the text.)*

Results

Our findings are shown in the Table and in Figs 1 to 5. All patients had abnormally prolonged monophasic action potential duration in comparison with the values found in patients with regular sinus rhythm (Olsson, 1971, 1972). Differences in duration of the monophasic action potential, recorded at various ventricular sites, were between 120 and 175 ms in cases 2 and 3, and in case 1 no such differences could be found. In cases 2 and 3 there was a second deflection (0_1) during the late repolarisation phase in the monophasic action potential recordings (Fig. 4C and Fig. 5C and D). Such differences between recordings in the same subject are an unusual finding, as are the differences in the shape of the recordings from one site to the other. Refractory periods were also prolonged (Fig. 3C), and differences between the effective refractory periods recorded in the various parts of the right ventricle were also abnormal in comparison with previous data obtained in man (Guss *et al.*, 1976).

Discussion

Several types of the long QT syndrome have been

Table *Data obtained with right ventricular MAP recordings and right ventricular refractoriness in 3 patients with long QT syndrome*

Case no.	*Cycle length (ms)*	*QT interval (ms)*	*QT$_c$ interval (ms)*	*RV MAP 90 per cent (ms)*			*RV ERP (ms)*			*Aetiology*
				A	*B*	*C*	*A*	*B*	*C*	
1	1000 (SR)	700	0·70	525	525	525	—	—	—	Quinidine
	880	650	0·69	500	500	500	420	420	—	
	750	610	0·71	475	475	475	400	400	—	
2	750 (SR)	530	0·58	480	365	360	—	—	—	Congenital
	710	520	0·61	470	350	370	415	310	350	
	650	480	0·60	450	325	355	395	295	325	
3	1200 (SR)	600	0·55	460	370	510	—	—	—	Congenital
	950	550	0·56	450	350	500	385	295	—	
	850	600	0·65	430	325	400	370	285	—	

Abbreviations: A, B, and C represents different recording sites from lateral wall (A), base (B), and apex and septal wall (C) of the right ventricle;
RV ERP, right ventricular effective refractory period;
RV MAP, right ventricular monophasic action potential;
SR, sinus rhythm.

described: the heritable syndrome, with or without deafness, and the acquired forms. The basis of the congenital syndrome has been assumed to lie in pathological changes in the conducting tissue (Phillips and Ichinose, 1970) or in functional modifications caused by abnormalities in the repolarisation of the myocardial fibres secondary to metabolic disturbances (Schwartz *et al.*, 1975), by an abnormal response to neurogenic stimuli, or an asymmetrical sympathetic stimulation of the ventricular muscle (James, 1969). The acquired long QT syndrome is secondary to conditions associated with bradycardia, hypokalaemia, or the use of drugs like quinidine, amiodarone, imipramine, and others (Motté *et al.*, 1970). The suggested mechanism for the acquired long QT syndrome is a diffuse myocardial desynchronisation which is a contraindication to the administration of antiarrhythmic drugs such as propranolol, ventricular pacing being the treatment of choice in such cases (Schwartz *et al.*, 1975). There are few electrophysiological studies in this syndrome. Wellens *et al.* (1972) described a girl with the congenital syndrome who developed ventricular fibrillation on arousal from sleep by auditory stimuli. Functional refractory periods of both ventricles were within normal limits, the greatest difference between various ventricular sites being 35 ms. In our cases, however, right ventricular monophasic action potentials showed a distinct prolongation in comparison with the values found by Olsson in patients with regular sinus rhythm. Data from human ventricular refractoriness (Guss *et al.*, 1976) suggested that our findings were also abnormal showing a considerable prolongation. That monophasic action potential prolongation was not artefactual, caused by changes in the intensity of suction applied during the recording procedure, is shown by the concurrent variations in right ventricular monophasic action potential duration and refractory periods measured with the help of the pacing technique. The asynchrony in refractoriness of ventricular muscle is suggested in our cases by the great differences between monophasic action potential recordings and refractoriness from various sites. The lack of such differences in the case described by Wellens may be explained by the fact that the QT changes occurred transiently preceding the syncopal attack, and the electrophysiological study was done while the QT interval was not greatly prolonged. In our patients the monophasic action potential recordings were performed during the period when QT prolongation was manifest. It is of interest to note that dispersion of repolarisation shown by monophasic action potential recordings was present in cases 2 and 3 with congenital long QT syndrome, while in case 1 with quinidine syncope, where the QT interval returned to normal after a few days, there was uniform prolongation of the right ventricular monophasic action potential duration. A prolongation of right atrial monophasic action potential under the effects of quinidine has been noted in man (Gavrilescu *et al.*, 1972, 1976). In the dog quinidine prolongs right atrial and ventricular monophasic action potentials and also lengthens the refractory periods (Comşulea *et al.*, 1976). However, in comparison with these data, the duration of the monophasic action potential and refractoriness of the right ventricle were excessively prolonged in our patient.

Abnormal monophasic action potentials may also explain changes in the T wave during the long QT syndrome. It has been shown experimentally that small monophasic action potential duration changes are associated with T wave modifications (Autenrieth *et al.*, 1975a, b). There may be an uneven contribution of different repolarisation regions to the T wave shape. The type of monophasic action potential shown in Fig. 4C and Fig. 5C and D with a second deflection was observed in two cases. Though this deflection could be considered to be an artefact resulting from displacement of the catheter or modification of suction during the recording period, we believe that such a tracing is caused by delayed repolarisation of some myocardial zones, adjacent to the exploring electrode. This assumption is supported by the fact that the suction pressure was constant, the tracings were stable, and the longest monophasic action potential duration recorded in such cases was very close to the sum of both recorded complexes (0 and 0_1 in Fig. 4C and Fig. 5C). This phenomenon could be accentuated by variations of the cycle rate (Fig. 5D). The appearance of ventricular arrhythmias during the long QT syndrome may be triggered by critical differences of refractoriness between various ventricular areas. However, in case 1, where the long QT syndrome was caused by quinidine this non-uniformity of electrophysiological events was not evident. We can not exclude the existence of such differences in the entire ventricular myocardium because of the limitations of the method. Although our studies cannot explain the detailed mechanism of the long QT syndrome, they allow the demonstration of uneven and delayed repolarisation of the ventricular myocardium as the common pathogenic mechanism of this syndrome.

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Loss of electrically active myocardium during inferior infarction in man[1]

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SUMMARY Serial 72 point praecordial electrocardiographic maps were recorded in 19 patients who suffered from uncomplicated inferior myocardial infarction. The natural history of ST segment elevation and of regional loss of R waves and development of Q waves were recorded. Plasma MB creatine kinase activity was measured at intervals during the first four days after the onset of chest pain.

The electrocardiographic maps showed that the praecordial area of ST segment elevation reached a maximum within 1 hour then diminished rapidly and disappeared in 18 of the 19 patients within 7 days after the onset of chest pain. The regional loss of R waves occurred within 6 hours from the onset of pain. The praecordial area of Q waves appeared in the second hour and was fully developed within 12 hours after the onset of chest pain.

Electrocardiographic changes indicating loss of electrically active myocardium were almost complete before MB creatine kinase activity appeared in the plasma. The timing of electrocardiographic events in relation to the onset of symptoms and to the detection of cardiospecific enzyme activity in the blood may be important in deciding when to make therapeutic interventions and how to assess their effects on the progressive loss of active myocardium during acute infarction of the heart.

There were reciprocal and complicated electrocardiographic manifestations of posterior and/or lateral myocardial involvement in these patients. In addition the praecordial area of ST segment elevation showed rapid resolution in the 4 hours after the onset of pain. For these reasons there was no simple relation between areas of ST segment elevation, the loss of R wave amplitude, and the appearance of Q waves in these patients with inferior myocardial infarction.

It is important to understand the pattern and time course of the electrocardiographic manifestations of necrosis during acute cardiac infarction before one can assess treatments aimed at conserving viable myocardium. Recent research has shown the progressive changes in praecordial ST segment elevation, R wave loss, and the development of Q waves in electrocardiographic maps during uncomplicated anterior infarction (Selwyn and Shillingford, 1977; Selwyn *et al.*, 1977).

In this investigation, the praecordial electrocardiographic manifestations of ischaemia (ST segment elevation) and cell death (R wave loss and development of Q waves) were followed during acute inferior myocardial infarction. The relation between the onset of chest pain, the electrocardiographic abnormalities, and the appearance and disappearance of plasma MB creatine kinase activity has been studied.

Methods

PATIENTS

Nineteen patients (14 men and 5 women, aged from 37 to 68 years (mean 57 years)) were studied after admission to the coronary care unit at the Hammersmith Hospital with a clinical diagnosis of acute inferior myocardial infarction. All these patients developed typical serial electrocardiographic abnormalities of acute inferior myocardial infarction on the routine 12 lead electrocardiogram, had a diagnostic rise in serum enzymes, and had an uncomplicated course after admission. None developed (a) recurrent chest pain lasting more than 5 minutes

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that was separate from the initial episode, (b) clinical or chest *x*-ray evidence of congestive heart failure or pulmonary oedema, or (c) cardiac rhythm disturbances other than unifocal isolated ventricular ectopic beats.

Praecordial electrocardiographic maps were recorded on admission (when this was less than 1 hour), 1 hour after the onset of chest pain, then 4 hourly for 12 hours, and daily thereafter. Additional observations were made if the clinical condition changed. Four patients were seen within the first hour after the onset of chest pain, a further 10 presented between 1 and 4 hours, and 5 presented between 4 and 6 hours after the onset of pain. Electrocardiograms were recorded using a direct writing ink jet Mingograf (Elema-Schonander) recording on 3 channels simultaneously. The gain employed was 10 mm for 1 mV and the paper speed was 25 mm per second. The electrodes were the Welsh suction type with a contact diameter of 1 cm. Electrocardiograms were recorded from 72 points distributed evenly over the praecordium as described by Reid *et al.* (1971).

The TP segment was used as the isoelectric line, or the PQ segment when the TP segment was difficult to locate because of tachycardia. ST segment elevation was measured in millimetres to the nearest 0·5 mm at 0·06 s after the nadir of the S wave. At each electrocardiographic position the R and S waves were measured in mm to the nearest 0·5 mm and the R/S ratio was calculated. R wave height alone was used when the S wave measured less than 0·5 mm. Praecordial maps were always recorded with the patients at rest and reclining at 45°.

The appearance of QRS widening, bundle-branch block, or pathological axis changes can alter the interpretation of these electrocardiographic signs (Massie and Walsh, 1960; Beckwith, 1970). Patients whose electrocardiograms showed QRS widening beyond 110 ms, or axis changes beyond $-30°$ and $+120°$ in the frontal plane were excluded from this study. Pathological Q waves were identified using the Minnesota Code criteria (Blackburn *et al.*, 1960; Rose and Blackburn, 1968). QR waves were identified as those complexes showing pathological Q waves but with dominant R waves, and Qr waves were defined as those complexes showing r waves smaller than the accompanying pathological Q waves.

A test of the reproducibility of praecordial mapping has already been published (Selwyn and Shillingford, 1977; Selwyn *et al.*, 1977). The surface maps produced in this way from patients suffering acute infarction showed areas of (1) ST segment elevation greater than 2 mm; and (2) Q, Qr, and QR waves.

Praecordial maps from each patient at each time interval were used to calculate the sum of all the Q waves measured in mm (ΣQ) and to count the number of positions showing Q, QR, and Qr waves in the 72 point map (area Q). Each map was also used to calculate the sum of all the ST segment elevation in mm (ΣST) and the number of praecordial positions showing ST elevation of more than 2 mm. The 72 electrocardiographic complexes in each praecordial map were used to calculate a mean value for R/S (R wave amplitude in mm was used where S waves were $< 0·5$ mm).

A multiple analysis of variance was used to test the significance of changes seen in the praecordial maps. This takes into account the importance of variables resulting from non-cardiac events (e.g. respiration and posture).

Five millilitre venous blood samples (taken at 3-hourly intervals for the first 24 hours after onset of chest pain, then 6 hourly for 4 days) were drawn from each patient into lithium heparin tubes and centrifuged at 2000 g for 10 minutes. Total plasma CK activity was measured spectrophotometrically (using Cecil 272 system spectrophotometer, Cecil Instruments, Cambridge) by the method of Oliver (1955) as modified by Hearse *et al.* (1973). Using this method the upper limit of plasma CK activity for healthy subjects is 50 mU/ml (Ogunro *et al.*, 1976).

Samples with activity greater than 250 mU/ml were diluted before determination of total CK. In order to minimise the dilution-activation effect observed with plasma CK, heat inactivated plasma was used as diluent (Graig *et al.*, 1967).

Isoenzymes of CK were separated by electrophoresis on agarose gel and quantified in aqueous solution by fluorometry (Ogunro *et al.*, 1976). The plasma activity of the MB-isoenzyme of CK was plotted against the time after the onset of chest pain to show the appearance and disappearance of this cardiospecific isoenzyme in the circulation.

Results

The typical changes in the praecordial electrocardiographic signs of ST segment depression and elevation are shown in Fig. 1. The praecordial area and height of ST segment elevation reached a maximum within the first hour after the onset of chest pain. Both decreased significantly thereafter and disappeared in 5 patients within 8 hours. A further 6 patients lost all ST segment elevation between 8 and 24 hours, and within 7 days from the onset of chest pain 18 of the 19 patients had no significant praecordial ST segment elevation (Fig. 2). The analysis of variance showed that the changes in the prae-

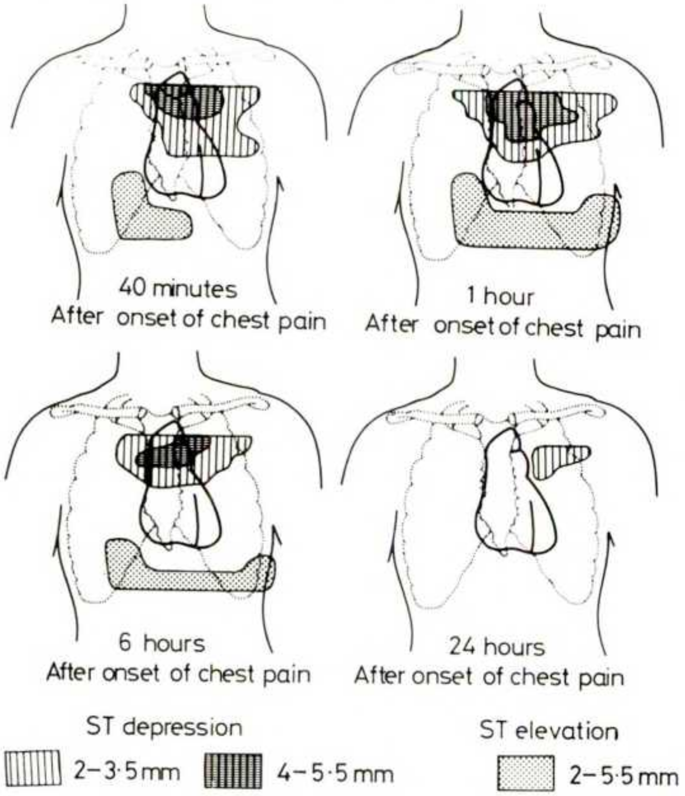
40 minutes
After onset of chest pain
1 hour
After onset of chest pain
6 hours
After onset of chest pain
24 hours
After onset of chest pain
ST depression
2–3·5 mm
4–5·5 mm
ST elevation
2–5·5 mm

Fig. 1 *Serial praecordial electrocardiographic maps showing typical changes seen in the area of ST segment elevation outlined during acute inferior myocardial infarction.*

cordial area of ST segment elevation after 1 hour from the onset of pain were highly significant ($P < 0{\cdot}001$).

The praecordial R/S showed an initial increase in R wave amplitude ($n = 4$). This was followed by a rapid loss of R waves and a development of Q waves, which were complete within 12 hours from the onset of chest pain in all 19 patients (Fig. 3). A typical example of the pattern of changes in RS ratios, QR, and Q waves is shown in Fig. 4. An example of the changes in RS ratio (showing increase in R wave amplitude) seen in the mid and upper areas of the

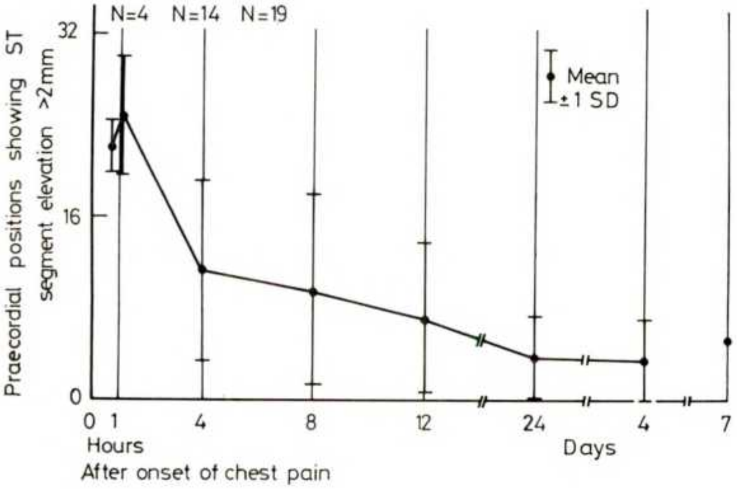

Fig. 2 *The praecordial area of ST segment elevation (number of positions showing ST change > 2 mm) reaches a peak within 1 hour and diminishes rapidly after the onset of chest pain.*

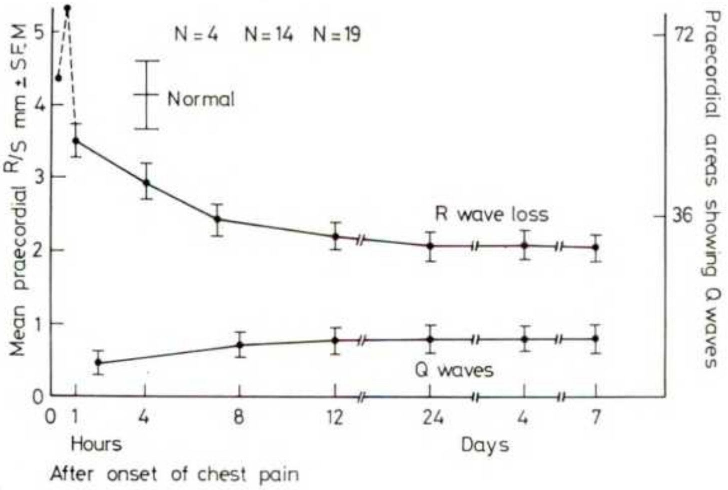

Fig. 3 *The mean praecordial RS ratio changes showed a progressive loss of R wave after the onset of chest pain in 19 patients suffering inferior myocardial infarction. The development of the praecordial area of Q waves is also shown.*

praecordial maps in 7 of these patients is shown in Fig. 5. The praecordial positions involved showed 36 ± 4 per cent increase in RS ratio or R wave amplitude. When the mean praecordial R/S ratios were calculated the temporary regional increases in R wave amplitude were included.

In the 14 patients studied within 4 hours from the onset of chest pain the praecordial electrocardiographic positions showing ST segment elevation between 2 and 4 mm lost 42 ± 27 per cent (mean ± SD) of R wave amplitude and 16 ± 3 per cent of these positions showed pathological Q waves at 24

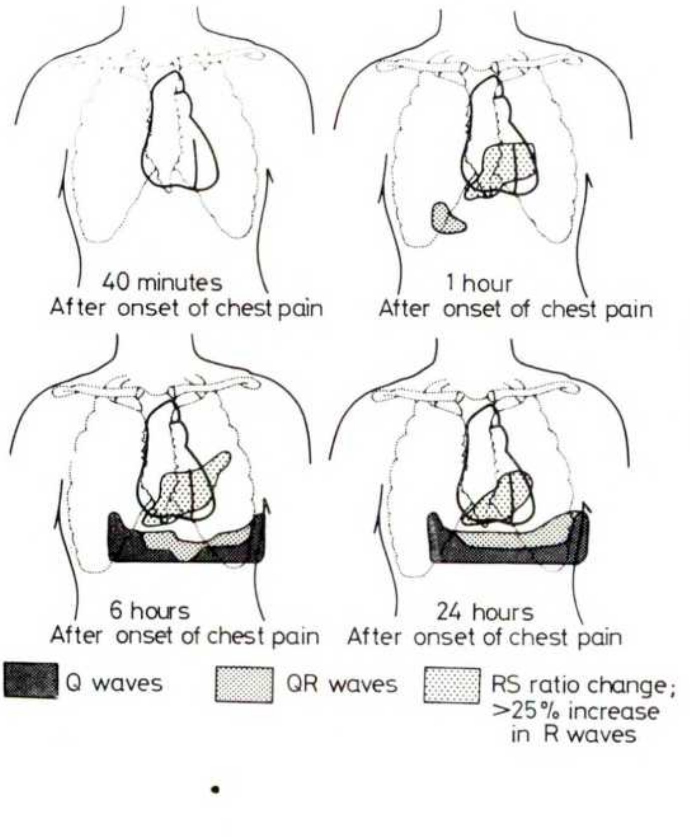
40 minutes
After onset of chest pain
1 hour
After onset of chest pain
6 hours
After onset of chest pain
24 hours
After onset of chest pain
Q waves
QR waves
RS ratio change; >25% increase in R waves

Fig. 4 *A typical example of the praecordial regional loss of R wave electromotive force and development of Q waves during inferior myocardial infarction. An area showing reciprocal simultaneous increases in R wave amplitude is shown.*

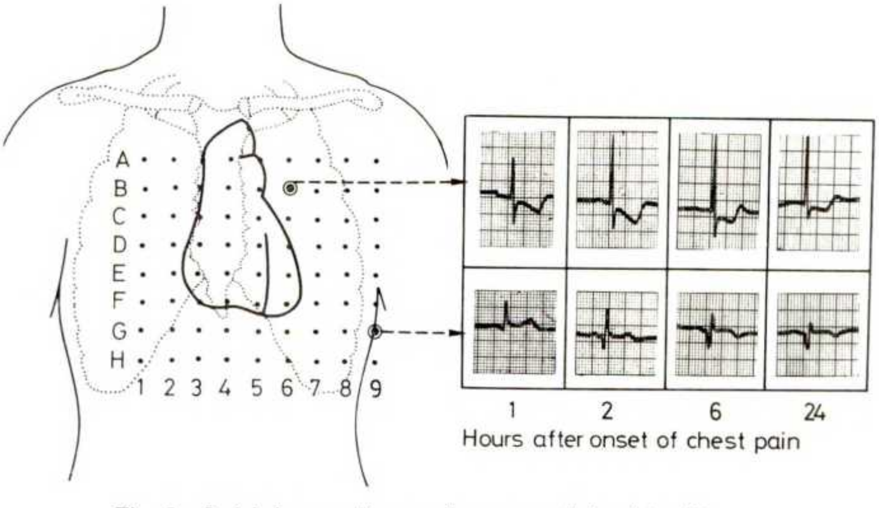

Fig. 5 *Serial electrocardiograms from praecordial position G9 showing the loss of R and development of Q waves and serial electrocardiograms from position B6 show reciprocal changes after the onset of chest pain. These were not seen in the routine 12 lead electrocardiogram.*

hours. The praecordial positions showing ST segment elevation of between 4 and 10 mm within 4 hours lost 79 ± 24 per cent of R wave amplitude and 32 ± 5 per cent of these showed Q waves at 24 hours. There was no relation between the early praecordial areas of ST segment elevation at 2 to 4 hours and the later areas of R wave loss and/or Q waves.

MB creatine kinase activity was detected in the plasma at 6 hours (median 6 hours, interquartile range 5·4 to 6·4 hours with 90% confidence limits for the median of 5·5 to 6·4 hours; $n = 19$). Maximum MB CK activity (range 80-251 mU/ml) was measured at 19·4 ± 1·7 hours (mean ± SD) and all detectable activity was cleared from the plasma by 58 ± 5·3 hours after the onset of chest pain.

Discussion

This study has shown that the praecordial area of ST segment elevation reached a peak within 1 hour and then diminished rapidly and disappeared within 7 days in 18 of the 19 patients. R wave loss and the development of Q waves were noted in the 2nd hour and progressed to complete development within 12 hours from the onset of chest pain. In 7 patients an area showing significant increases in R wave amplitude was outlined in the middle and upper portions of the praecordial maps and was accompanied by ST segment depression. This occurred during the loss of electrically active myocardium recorded in the lower portions of the maps and probably represented reciprocal changes in the anterior electrocardiographic forces because the posterior aspect of the heart was involved during the myocardial infarction. This electrocardiographic sign was not detectable in the routine 12 lead electrocardiogram in 4 of the 7 patients studied.

The praecordial electrocardiographic signs of inferior myocardial infarction were complicated. Praecordial ST segment elevation resolved rapidly so that within 4 hours this manifestation of ischaemia could no longer be identified at many praecordial sites that subsequently lost R wave amplitude. The ST segment elevation, R and Q wave changes all had different natural histories. In these patients with inferior myocardial infarction characteristic ST segment elevation and changes in R wave amplitude were accompanied and influenced by the electrocardiographic abnormalities of posterior and/or lateral myocardial involvement. The praecordial positions showing pathological ST segment elevation > 2 mm did lose R wave amplitude and develop Q waves. However, the indirect and incomplete projection of inferior infarcts was not associated with any simple relation between the early praecordial electrocardiographic manifestations of ischaemia (ST segment elevation) and the later electrocardiographic signs of cell death (Q waves).

Serial praecordial mapping of the electrocardiogram during anterior myocardial infarction can provide a non-invasive assessment of changes in a number of well-known electrocardiographic signs. Previous studies have shown that only tracings recording during sinus rhythm can be used and the significant effects of posture, respiration, and other abnormalities of impulse conduction must be excluded (Selwyn and Shillingford, 1977; Selwyn *et al.*, 1977). These earlier studies showed the natural history of ST segment elevation, the regional loss of R wave electromotive force, and the development of Q waves during anterior infarction. The regional loss of electrically active myocardium occurred before MB CK activity was detected in the plasma and the praecordial area of ST segment elevation at 2 hours could reasonably predict the final area of Q waves at 24 hours after the onset of chest pain in each patient. In patients suffering anterior infarction both these factors may be important and useful in deciding when to administer interventions and how to assess their effects (Selwyn and Shillingford, 1977; Selwyn *et al.*, 1977).

In conclusion, praecordial mapping of the electrocardiogram in a group of patients suffering acute uncomplicated inferior myocardial infarction has shown that ST segment elevation is a rapidly changing electrocardiographic sign. The complex geometric factors influencing the projection of electrocardiographic signs from the heart onto the praecordium during inferior infarction invalidate the relation between a manifestation of acute regional myocardial ischaemia (praecordial area of ST segment elevation) and cell death (praecordial area of Q waves) in each patient. The regional loss of electrically active myocardium and development of Q waves is almost complete before MB CK activity appears in the plasma, and the praecordial areas showing reciprocal increases in R wave amplitude suggest posterior cardiac involvement and do not always show in the routine electrocardiogram.

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Prehospital sudden death from ischaemic heart disease

A postmortem study

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SUMMARY A detailed postmortem study of the myocardium and coronary arteries was performed on 114 men and 37 women who died suddenly outside hospital. Data on the disease history and certain risk factors were collected through an 'Ischaemic Heart Disease Register'.

Men and women did not differ with respect to history of previous symptoms of ischaemic heart disease or necropsy findings. A history of hypertension and the previous use of digitalis or diuretics tended to be more frequent in women than in men but current smoking was more common in men (69%) than in women (43%). Of the subjects in whom necropsy revealed an old myocardial infarction, 86 per cent had a history of symptomatic ischaemic heart disease but a previous myocardial infarction was known in only 42 per cent of them. A definite recent myocardial infarction was found in 26 per cent and an early infarction in 51 per cent. About half of the patients with a definite recent or an early myocardial infarction, and half of those with no recent myocardial infarct, died at once. Fourteen per cent of the subjects died after symptoms lasting 2 hours or more.

Triple vessel disease in the coronary arteries was found in 56 per cent of cases, double vessel disease in 31 per cent, and single vessel disease in 11 per cent. Aortic valvular stenosis or a history of hypertension was present in 3 cases with no obvious coronary disease. Suddenness of death did not correlate with severity of coronary obstruction. Arterial lesions were more severe in patients with an old myocardial infarction than in those without this. The more severe the coronary artery disease, the more likely a definite recent myocardial infarction was to be present. The mildest disease was found in patients with no detectable recent myocardial infarction.

No significant differences were found between patients with symptomatic and those with silent but definite myocardial infarction. Heavy smoking was most common in patients with an early recent myocardial infarction. Patients dying without warning and with no recent infarction (those with a primary arrhythmia) had severe coronary artery disease less frequently than those dying with a recent infarction. None of the former had been heavy smokers. They had, however, large scarred hearts, and a high incidence of previous hypertension, of ischaemic heart disease, and of treatment with digitalis or diuretics.

Sudden death is a major problem in ischaemic heart disease. Its aetiology is difficult to study, for without clinical data the diagnosis has to be based mainly on information at necropsy. The establishment of Ischaemic Heart Disease Registers according to the guidelines suggested by the World Health Organization has permitted the identification of all deaths from ischaemic heart disease within a defined community (Romo, 1973). Reliable collection of data concerning the fatal attack and the previous illnesses of a patient is also feasible (Siltanen, 1972).

The diagnosis of death from ischaemic heart disease is easy if an acute myocardial infarction has developed to the stage of a necrotic lesion. Difficulties arise when death occurs within a few hours of the onset of the attack, since uniform criteria have not been accepted for the pathological diagnosis of acute myocardial infarction. In order to resolve this problem a co-operative study by the WHO has been carried out. The preliminary results

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(World Health Organization, 1973), in which various methods of study previously proposed (World Health Organization, 1970) were tested and evaluated, indicated outlines for the pathological diagnosis of sudden death from myocardial infarction.

The present study was sponsored by the Ischaemic Heart Disease Register of Helsinki. Data concerning sudden death have been previously published in a report on all registered (Romo, 1973) and all fatal cases of ischaemic heart disease (Rissanen *et al.*, 1975). This paper deals with the subgroup of sudden deaths in which a postmortem study was performed using the methods proposed by the WHO, focusing the main attention on the presence of recent myocardial infarction and the prevalence of different coronary lesions or their combinations in relation to the course of the fatal attack.

Subjects and methods

Altogether, 365 deaths from ischaemic heart disease, outside hospital, were registered during a period of 12 months in Helsinki. Elderly subjects (aged 65 years or over) were studied for a period of 3 months only. A medico-legal necropsy using a special technique of examination of the heart was performed in 213 registered cases and those in this study consisted of 151 in whom the fatal attack was witnessed, the circumstances of the attack well documented, and in whom death occurred within 24 hours of the onset of the attack. There were 114 men aged between 31 and 83 years, and 37 women aged between 44 and 90 years.

DATA COLLECTION

Information about the fatal attack and previous illnesses was obtained from hospital records and from relatives. The principles of data collection have been described in detail in an earlier paper (Romo, 1973). Previous angina pectoris, myocardial infarction, dyspnoea on exertion, and hypertension were recorded using definitions by the World Health Organization (1976). Premonitory symptoms in the 28 days preceding death were noted. Medical care before death was assessed from the drugs taken by the patients, particularly digitalis, diuretics, and antihypertensives.

The patients were allocated into 4 categories according to smoking habits: (1) heavy smokers, that is those smoking 25 or more cigarettes a day; (2) other cigarette smokers; (3) ex-smokers, that is those who had given up smoking at least three months before death; and (4) non-smokers.

NECROPSY DATA

Medico-legal necropsies were performed at the Department of Forensic Medicine, University of Helsinki. The principles outlined by the World Health Organization (1970, 1973) were applied to the examination of the hearts. All necropsies were carried out by the same person (V.R.).

A double contrast modification of the postmortem coronary angiogram was developed to show changes in the coronary arteries (Rissanen, 1970), and in addition, they were opened longitudinally and examined carefully. The degree of coronary stenosis was estimated by these procedures. The right coronary artery (RC), left anterior descending coronary artery (LAD), and left circumflex coronary artery (LC) were each graded according to the maximum obstruction, using three scores: Score 0 = no stenosis or less than 50 per cent stenosis; Score 1 = a 50 per cent stenosis or more but no occlusion; Score 2 = occlusion.

The scores of the three vessels were added to give a stenosis score for the whole coronary arterial tree ranging from 0 to 6. A stenosis in the main trunk of the left coronary artery was classified as double vessel disease.

After angiography the heart was sliced from the apex to the base. The slices were stained by a macroscopic histochemical method (Nachlas and Shnitka, 1963) to show the infarcted areas, from which myocardial blocks for histological study were taken. When macroscopic examination was negative, blocks were taken from the anterior and posterior walls of the left ventricle and from the interventricular septum. Haematoxylin-eosin and phosphotungstic acid haematoxylin were used to stain sections. The principles of the WHO co-operative study (World Health Organization, 1973) were applied in the histological diagnosis of a recent infarction. The two stages of a recent myocardial infarction were defined as follows:

—*early myocardial infarction:* Macroscopic discoloration, pallor, or softening, and/or at least two of the following microscopic changes of the myocardium: (1) cytoplasmic hypereosinophilia, coagulation, clumping, alteration of striation (contraction bands), (2) loss of nuclei in the myofibres, (3) margination of polymorphonuclear leucocytes, (4) leucocytosis, or (5) oedema.

—*definite myocardial infarction:* Macroscopic necrosis, softening, or discoloration of the myocardium and microscopic infiltration of polymorphonuclear leucocytes in the area of necrosis with or without macrophages.

The recognition of a recent myocardial infarction was ultimately based on findings of the histological examination. A scar of 0·5 cm or more in diameter

Table 1 *Duration of fatal attack and history of previous angina pectoris, myocardial infarction, dyspnoea, and premonitory symptoms: distribution according to age and sex*

Age	*No. of cases*	*Suddenness of death*			*Angina pectoris*			*Infarction*			*Dyspnoea*			*Premonitory symptoms*		
		Inst.	*< 2 h*	*> 2 h*	*Data available*	*No.*	*%*	*Data available*	*No.*	*%*	*Data available*	*No.*	*%*	*Data available*	*No.*	*%*
Men																
30-44	9	5	4	—	8	1	12·5	8	1	12·5	7	6	86·0	8	6	75·0
45-54	30	12	11	7	28	17	61·0	28	8	29·0	24	14	58·0	26	18	69·0
55-64	56	32	17	7	51	36	71·0	51	18	35·0	52	37	71·0	52	31	60·0
65 or over	19	11	8	—	14	7	50·0	16	4	25·0	14	10	71·0	12	4	33·0
Total	114	60	40	14	101	61	61 0	103	31	30·0	97	67	69·0	98	59	60·0
Women																
40-54	8	7	—	1	6	3	50·0	7	1	14·0	6	5	83·0	6	4	67·0
55-64	19	10	6	3	16	12	75·0	18	6	33·0	16	12	75·0	16	9	56·0
65 or over	10	1	6	3	9	2	22·0	10	1	10·0	8	4	50·0	8	3	37·5
Total	37	18	12	7	31	17	55·0	35	8	23·0	30	21	70·0	30	16	53·0

was regarded as an old healed infarction (Guzman *et al.*, 1968).

After blood clots had been removed from the chambers, the heart was weighed. The presence of a fresh coronary thrombus was estimated visually from angiograms and/or the longitudinally opened coronary arteries but without histology.

Results

HISTORY OF FATAL ATTACK

According to the interviewers of the Ischaemic Heart Disease Register, 53 per cent of men and 49 per cent of women of this series died instantaneously at the witnessed fatal attack without showing prior symptoms (Table 1). Only 21 patients (14%) had symptoms for longer than 2 hours. In the remaining 52 (34%) death occurred within this period but even in the majority of these the duration of the episode was only a few minutes.

Eighty patients (53%) died at home, 32 (21%) on the way to hospital or at the outpatient department, and the remaining 39 elsewhere.

DISEASE HISTORY AND NECROPSY DATA

Previous symptoms (angina pectoris, dyspnoea, other premonitory symptoms) or a history of a previous infarction did not show any relation to age or sex (Table 1). The necropsy disclosed no clear influence of age or sex in the incidence of recent or old myocardial infarction, coronary occlusion or thrombosis, the range of the stenosis score, or the heart weight (Table 2). A history of hypertension and previous use of digitalis or diuretics was slightly more common in women than men (Table 3). This, however, was not statistically significant. Of the men, 69 per cent, and of the women 43 per cent had been current smokers (Table 3).

In all age groups the necropsy finding of old myocardial infarction (Table 2) was much more

Table 2 *Incidence of recent and old myocardial infarction, coronary occlusion, and thrombosis, and median (M) and range (R) values of stenosis score and heart weight, according to age and sex*

Age	*No. of cases*	*Recent infarction*				*Old infarction*		*Coronary occlusion*		*Coronary thrombosis*		*Stenosis score R(M)R*	*Heart weight R(M)R*
		Definite No.	*Initial No.*	*Total No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*		
Men													
30-44	9	1	6	7	78	5	56	7	78	6	67	1(*3*)6	410(*440*)630
45-54	30	12	15	27	90	17	57	24	80	17	57	1(*4*)6	350(*470*)880
55-64	56	11	30	41	73	40	71	45	80	23	41	0(*4*)6	340(*500*)820
65 or over	19	5	7	12	63	13	68	14	74	9	47	2(*4*)6	380(*470*)880
Total	114	29	58	87	76	75	66	90	79	55	48	0(*4*)6	340(*490*)880
Women													
40-54	8	2	4	6	75	2	25	2	25	2	25	0(*1*)5	310(*455*)610
55-64	19	6	8	14	74	12	63	14	74	5	26	1(*4*)5	320(*450*)620
65 or over	10	4	5	9	90	3	30	9	90	5	50	3(*4*)5	430(*465*)830
Total	37	12	17	29	78	17	46	25	68	12	32	0(*4*)5	310(*455*)830

Table 3 *History of hypertension, use of digitalis, and/or diuretics, and history of smoking habits in whole series*

	Men (total 114)			*Women (total 37)*		
	Data available	*No. of cases*	*%*	*Data available*	*No. of cases*	*%*
History of						
hypertension	92	28	30	29	14	48
use of digitalis or diuretics	90	32	36	28	14	50
Smoking habits	87			26		
heavy smokers		28	32		2	8
other smokers		30	35		9	35
ex-smokers		15	17		3	12
non-smokers		14	16		12	46

frequent than could be expected on the basis of the Ischaemic Heart Disease Register interviews (Table 1). A previous episode of clinical myocardial infarction was known about in only 38 of the 91 patients (42%) with a myocardial scar found at necropsy. Of the 53 patients with a scar but with no history of previous infarction, 40 had had angina pectoris or dyspnoea on exertion. The remaining 14 per cent of the subjects with an old infarction (12 men, 1 woman) had no history of clinical heart disease. Two of them had had hypertension, and 7 had been heavy smokers.

FATAL ATTACK IN RELATION TO A RECENT ISCHAEMIC MYOCARDIAL LESION

Necropsy showed a recent myocardial infarction in 77 per cent of all cases in the series. A definite myocardial infarction was present in 26 per cent and an early myocardial infarction in 51 per cent. A macroscopic recent myocardial lesion, if present, was nearly always limited to the subendocardial zone of the left ventricle. Anomalous crossband formations were characteristic of altered myofibres on microscopy in cases of early myocardial infarction.

The clinical suddenness of death did not show any clear relation to the stage of a recent ischaemic myocardial lesion. In about half the patients with a definite or an early infarction, as well as of those with no recent ischaemic lesion found at necropsy, the fatal attack ended abruptly (Table 4). Symptoms lasting over two hours were, however, more frequent in patients with a definite myocardial infarction.

DEGREE OF OBSTRUCTIVE CORONARY ARTERY DISEASE

Numerous combinations of obstructive changes in the three coronary arteries were found. The 9 most

Table 4 *Suddenness of death of persons with definite or initial myocardial infarction found at necropsy, and of those with no recent myocardial lesion*

Infarction	*No. of cases*	*Instantaneous death*		*< 2 hours*		*> 2 hours*	
		No.	*%*	*No.*	*%*	*No.*	*%*
Definite*	40	20	50	8	20	12	30
Initial	76	40	53	30	39	6	8
No recent MI	35	18	51	14	40	3	9

*Rupture in 5 cases (4 instantaneous deaths, 1 with symptoms over 2 hours).

Table 5 *The most common patterns of coronary stenosis in the total series, and in cases with and without an old infarction. RC = right coronary artery, LAD = left anterior descending coronary artery, LC = left circumflex coronary artery*

Total series (151 cases)				*With an old infarction (91 cases)*				*No old infarction (60 cases)*			
No. of cases	*RC*	*LAD*	*LC*	*No. of cases*	*RC*	*LAD*	*LC*	*No. of cases*	*RC*	*LAD*	*LC*
21	+	−	−	16	+	−	−	6	−	+	−
15	−	+	−	12	+	+	+	5	+	−	−
12	+	+	+	9	−	+	−	5	−	−	+
10	−	−	−	8	+	+	−	5	−	+	○
9	+	−	○	6	−	+	+	5	+	−	○
8	+	+	−	6	−	−	−	5	−	−	○
8	−	+	+	4	+	−	+	5	−	○	○
8	−	+	○	4	+	+	○	4	−	−	−
8	−	−	○	4	○	+	−	4	○	−	○
				4	+	−	○				
≤6	18 different combinations			<3	8 different combinations			<2	12 different combinations		

+ = an occlusion,
− = a 50% stenosis,
○ = no severe stenosis.

Table 6 *Percentages of triple, double, or single vessel disease or no coronary stenosis in present series and in 4 clinical series of patients with ischaemic heart disease studied by coronary arteriography*

Series	*Triple* %	*Double* %	*Single* %	*No disease* %
Present series				
Total	56	31	11	2
With old myocardial infarction	69	28	2	1
With no old myocardial infarction	37	37	23	3
Clinical series				
Webster *et al.* (1974)	38	38	24	
Burggraf and Parker (1975)	31	41	28	
Fuster *et al.* (1975)				
Angina pectoris	31	37	24	
Subendocardial myocardial infarction	42	40	13	
Transmural myocardial infarction	38	30	27	
Hekali (1976)	31	41	28	

common patterns of stenosis constituted two-thirds of all cases (Table 5). A severe stenosis in the main left coronary artery was found in 7 patients. Only 3 had no coronary stenosis of any severity. There were distinct differences in the pattern of disease between patients with an old infarction and those without one. In the former, triple vessel disease was more common and single vessel disease less common (Table 6). Coronary occlusion was found in 87 per cent of patients with a myocardial scar at necropsy and in 58 per cent of those with no scar. An occlusion in all three coronaries was found in 12 cases (8%), each patient with an old myocardial infarct.

The obstructive changes in the coronary arteries were no different in patients who died suddenly than in those who died after a period of symptoms, whether under or over two hours (Fig. 1). The three patients with no major stenosis all died without warning.

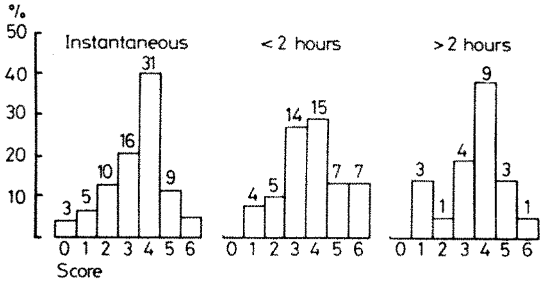

Fig. 1 *Stenosis scores in sudden deaths and in cases with a fatal attack of under or over 2 hours in duration. The figures above the columns indicate the number of cases.*

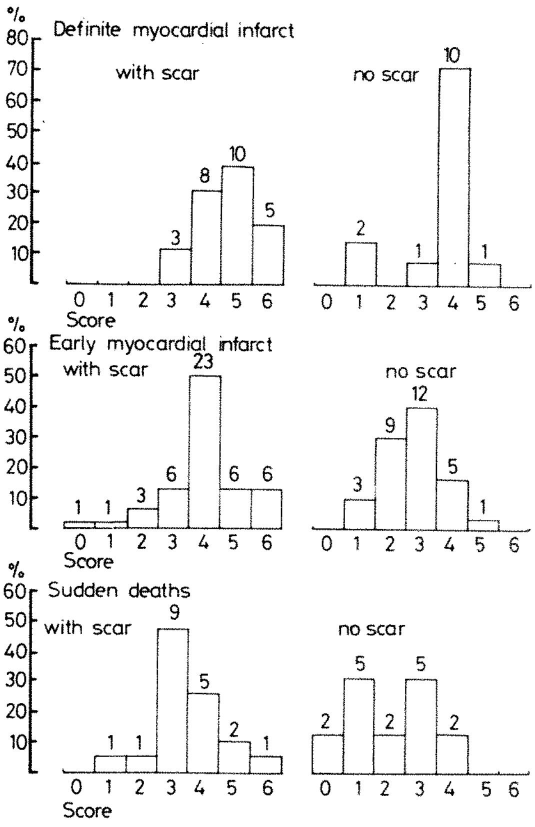

Fig. 2 *Stenosis scores in cases with a definite or an early myocardial infarction and in cases of sudden death with no recent myocardial lesion.*

Whether or not an old infarction had occurred coronary artery disease was most severe in patients in whom a definite recent myocardial infarction was found at necropsy, and least severe in those with no recent myocardial lesion (Fig. 2).

Of the 32 patients, 29 (91%) with the highest stenosis scores of 5 and 6 had a history of previous myocardial infarction, angina pectoris, or dyspnoea. In 30 of them a myocardial scar was found at necropsy. Low scores of 0 and 1, that is no coronary stenosis or a 50 per cent stenosis in one vessel, were found in 10 per cent of the cases; these coronary patterns were rare in subjects with a recent infarction (5%) but commoner in those without one (23%) ($P < 0{\cdot}01$). The low score values were also less frequent in subjects with an old infarction (3%) than in those without one (20%) ($P < 0{\cdot}001$). They were commoner in women (22%) than in men (7%) ($P < 0{\cdot}01$). The highest frequency of scores 0 and 1 was found in patients with neither recent nor old myocardial lesions (44%).

Table 7 *History and necropsy findings in cases of 'late', 'early', 'silent' acute myocardial infarction and 'primary arrythmia' (see text for definitions)*

	Late AMI			*Early AMI*			*Silent AMI*			*Primary arrhythmia*		
No. of cases, total	12			30			20			18		
Mean age (y)	58·5			58·8			62·7			56·3		
Age range	46-90			41-84			44-86			40-65		
Men/Women	8/4			23/7			14/6			14/4		
	Data available	*No. of cases*	%	*Data available*	*No. of cases*	%	*Data available*	*No. of cases*	%	*Data available*	*No. of cases*	%
History of												
Angina pectoris	11	9	82	26	15	58	18	10	56	17	14	82
Myocardial infarction	10	3	30	27	6	22	18	6	33	17	8	47
Dyspnoea	11	8	73	24	16	67	17	14	82	16	13	81
Prodromal symptoms	10	8	80	24	12	50	17	10	59	18	11	61
Use of digitalis or diuretics	8	3	38	26	5	19	16	7	44	17	13	77
Hypertension	11	4	36	27	7	26	17	6	35	18	9	50
Necropsy findings of												
Old myocardial infarction	12	8	67	30	19	63	20	12	60	18	13	72
Stenosis score $\geqslant 4$	12	10	83	30	17	57	20	17	85	18	5	28
Cardiac hypertrophy*	12	8	67	30	9	30	20	14	70	18	13	72
History of myocardial infarction/myoc. scar		3/6			6/18			6/11			8/13	

* $\geqslant 500$ g in men, $\geqslant 450$ g in women.

ACUTE MYOCARDIAL INFARCTION—PRIMARY ARRHYTHMIA

The correlation between clinical symptoms during the fatal attack and ischaemic myocardial lesions seen after death was poor. Accordingly the following subgroups were studied: (1) 'late' deaths from acute myocardial infarction: patients whose fatal attack lasted longer than 2 hours and in whom the ischaemic myocardial lesion had developed to the stage of a definite infarction; (2) 'silent' deaths from acute myocardial infarction: patients who died suddenly but in whom a definite myocardial infarction was found at necropsy; (3) 'early' deaths from acute myocardial infarction: patients who had symptoms for less than 2 hours and in whom necropsy disclosed an early ischaemic myocardial lesion; (4) deaths from 'primary arrhythmia': patients who died suddenly with no recent myocardial lesion at necropsy.

No significant differences were found in the incidence of symptomatic ischaemic heart disease, hypertension, or the use of drugs in the 'late', 'silent', and 'early' death groups (Table 7), but subjects in the early death group were less likely to have big hearts ($\geqslant 500$ g in men, $\geqslant 450$ g in women) than those in the other two ($P < 0{\cdot}01$) and severe coronary obstruction was also less common ($P < 0{\cdot}05$). This group showed the highest incidence of current smokers, and of heavy smokers (Table 8).

There were certain differences between the

Table 8 *History of smoking habits in cases of 'late', 'early', and 'silent' acute myocardial infarction and 'primary arrhythmia' (see text for definitions)*

	Late AMI		*Early AMI*		*Silent AMI*		*Primary arrhythmias*	
Data available	9		19		15		15	
	No. of cases	%	*No. of cases*	%	*No. of cases*	%	*No. of cases*	%
Current smokers	6	67†	17	90*	10	67†	4	27
Heavy smokers	4		12		4		0	
Other smokers	2		5		6		4	
Ex-smokers	1	11	1	5	2	13	5	33
Non-smokers	2	22	1	5	3	20	6	40

*Significant difference between early AMI and primary arrhythmia; $P < 0{\cdot}001$.
†Significant difference between late + silent AMI and primary arrhythmia; $P < 0{\cdot}05$

subjects dying from acute myocardial infarction and those in whom death probably resulted from a 'primary arrhythmia', that is those who died suddenly and had no acute ischaemic myocardial lesion (Table 7). Previous hypertension was more common in the arrhythmia group and digitalis or diuretics had been given more often (77%) compared with 30 per cent ($P < 0{\cdot}001$). Cardiac hypertrophy was also significantly more frequent ($P < 0{\cdot}05$). Severe obstructive coronary arterial disease, however, was significantly less in this group than in those with late or silent infarction ($P < 0{\cdot}001$). Smoking was not a characteristic feature of subjects who died from a 'primary arrhythmia' (Table 6).

Within the 'primary arrhythmia' group only 7 subjects (5%) had no definite evidence of ischaemic heart disease, that is no suggestive history, no myocardial lesion, and no coronary occlusion or thrombosis at necropsy. Two of them had aortic stenosis, and 2 a history of hypertension with pronounced cardiac hypertrophy. In the absence of ischaemic heart disease or a condition causing pronounced cardiac hypertrophy, therefore, an arrhythmia appears to be a rare cause of sudden death.

Discussion

The present series of sudden deaths is selected, including only those necropsies in which a particular technique was used, and excluding any case in which the fatal attack was unwitnessed. The latter clearly excluded many cases who died quickly and may have influenced the frequency of detectable acute infarction at necropsy. Despite this, some general conclusions on the characteristics of sudden death can be drawn, for example with regard to the distribution of coronary lesions, but the small number of cases in some comparisons must make interpretation tentative. The diagnosis of death from ischaemic heart disease is based mainly on the demonstration of a recent ischaemic lesion in the myocardium. It has been suggested that such lesions should be divided into two types: (1) myocardial infarction; a localised and discrete area of muscle necrosis in the myocardium visible to the naked eye and several centimetres in diameter and (2) diffuse subendocardial necrosis; circumferential myocardial necrosis involving the inner zone of the whole left ventricle (Davies *et al.*, 1976). In the present study the classification of recent ischaemic myocardial lesions was based on the microscopical changes in the myocardium. While many would accept as an acute myocardial infarction only those lesions with foci of polymorphonuclear leucocytes within the area of the necrotic myofibres or more advanced microscopical changes (Scott and Briggs, 1972; Baroldi *et al.*, 1974), that is, criteria comparable with ours of a definite infarction, the histological changes taken as indicators of an early infarction by us, though not specific, were suggestive of very recent ischaemic myocardial injury (World Health Organization, 1973).

In relation to the acute ischaemic event, about half the deaths occurred during the earliest stages of myocardial injury and a quarter when frank infarction had taken place while the remainder resulted from a primary arrhythmia often before any infarction at all. Though most sudden deaths seemed to occur at a very early phase of the acute myocardial infarction, it was obvious that in many cases the acute infarction had either been silent, misinterpreted, or ignored. When death occurred at the stage of frank infarction, coronary artery disease tended to be severe, and vice versa. It is possible that myocardial adaptation to chronic coronary obstruction influenced the course of the ischaemic attack, the patients with severe coronary lesions being those who had avoided fatal arrhythmias during the earliest stage of myocardial injury by the development of collaterals. According to Baroldi (1975) the presence of 'contraction bands' in a myofibre means that it has died in a hypercontracted state, and the finding of this in cases of early myocardial infarction supports the concept of a possible role of catecholamines or sympathetic overstimulation in the pathogenesis of sudden death (Baroldi, 1975).

In the study of the IHD Register of Helsinki a history of hypertension was most common in those dying suddenly and lowest in the survivors of acute myocardial infarction (Romo, 1973), and other studies have shown that hypertension in patients with ischaemic heart disease increases the risk of death, particularly sudden death (Beck and Hochrein, 1974; Burggraf and Parker, 1975; Kornitzer *et al.*, 1975). In the pooled Helsinki register findings a history of hypertension was nearly twice as frequent in women with acute ischaemic heart disease as in men (World Health Organization, 1976). A similar sex difference was found in the present study though without the same level of significance because of the size of the series. Population studies in Finland have also shown a higher incidence of hypertension in women than in men in middle age (Aromaa, 1974). In the present study hypertensives were found more frequently than in the Finnish population (Aromaa, 1974), and may explain a number of the sudden deaths without definite pathological evidence of ischaemic heart disease. Patients dying suddenly without complaining of symptoms indicative of an ischaemic attack, and in whom no ischaemic lesion was found in the myocardium, probably died of an arrhythmia. About 10 per cent of the cases fell into this category. These patients were not heavy smokers nor did they have severe coronary arterial disease. A history of hypertension, of the clinical symptoms of ischaemic heart disease, and of treatment with digitalis or diuretics was common. Their hearts tended to be enlarged and scarred and this, in the absence of severe coronary lesions, suggests that ischaemic heart disease in these subjects was of a different character from that in the patients who died with a detectable infarction. The use of digitalis and diuretics may simply reflect poor myocardial function. Alternatively, hypokalaemia following diuretic therapy may have caused arrhythmias such as ventricular ectopic beats or ventricular tachycardia in ischaemic subjects (Dyckner *et al.*, 1975).

Another factor increasing mortality in patients with ischaemic heart disease is smoking (Rose, 1973; Wilhelmsson *et al.*, 1975), and heavy smoking seems to be related to sudden death (Romo, 1973). Current smokers were overrepresented in the present series compared with the general Finnish population (Rimpelä *et al.*, 1975), and heavy smokers were common in the group in which death occurred a short time after the onset of infarction. On the other hand, heavy smoking was not characteristic of patients who died suddenly without infarction. Smoking, therefore, exerts a harmful influence via ischaemia rather than a tendency to arrhythmia, but may, however, favour the development of arrhythmias at the early stage of an ischaemic myocardial injury. It has been shown that the stimulation threshold for provocation of ventricular fibrillation decreases in laboratory animals inhaling tobacco smoke (Bellet *et al.*, 1970).

Severe obstructive coronary artery disease is characteristic of prehospital sudden deaths as well as of deaths from acute myocardial infarction in hospital (Rissanen *et al.*, 1975). The patterns of coronary stenosis varied considerably in the present series, with triple vessel disease with the major occlusive site in either the right or left anterior descending coronary artery being common. Patients with and without an old myocardial infarction also differed, the occlusive disease being more severe in the former than in the latter. A similar difference has also been found in quantitative studies of coronary atherosclerosis (Rissanen, 1975). The prognosis of single vessel disease has been shown to be better than that of double or triple vessel disease (Webster *et al.*, 1974; Burggraf and Parker, 1975) but in our patients without myocardial scarring coronary artery involvement was similar to that reported in many clinical series studied by coronary arteriography (Table 6). In patients with an old myocardial infarction, however, severe triple vessel disease was commoner than in clinical series. Clearly these patients were a self-selected group at a final stage. An important question remains; did a previous attack of infarction enhance the development of coronary artery disease in these patients? An infarction, even if the patient survives, causes deterioration both by myocardial damage and by the thrombotic obstruction of the artery supplying the infarcted area (Fuster *et al.*, 1975; Davies *et al.*, 1976). The concept of mural thrombi as the major factor in plaque growth and production of stenosis is now gaining general acceptance (Roberts, 1973). Alternatively, previous infarctions are more likely to have occurred in patients with the severest coronary artery disease.

No particular pattern of coronary lesion was characteristic of any of the clinical types of sudden death but a high incidence of severe involvement of the right coronary artery seems to be a common finding (Rissanen *et al.*, 1975). An important function of clinical studies is to show which coronary lesions carry a risk legitimately correctable by surgery: a severe stenosis in the left main coronary artery is one generally accepted (Burggraf and Parker, 1975; Julian, 1975). This region was significantly obstructed in only 5 per cent of our patients, a similar incidence to that reported by Fuster *et al.* (1975) in patients with myocardial infarction (5%) or with angina (8%).

Attention has recently focused on angina pectoris and myocardial infarction in patients with no coronary stenosis. Several unusual conditions have been listed as a cause of such infarction (Cheitlin *et al.*, 1975). Long-term observations in this group have shown a favourable prognosis (Bemiller *et al.*, 1973). Aortic valvular stenosis, and hypertension with cardiac hypertrophy were found in the 3 cases of sudden death without coronary artery disease in the present series.

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Congenital heart disease associated with hypertrophic cardiomyopathy

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SUMMARY Experience has shown that clinical hypertrophic cardiomyopathy (HOCM, ASH) occurs in some patients with congenital heart disease, particularly simple lesions with a good natural prognosis. Its presence should be suspected when the clinical course is atypical for the basic congenital lesion or when there is unexpected cardiomegaly, an associated left sided lesion or left ventricular hypertrophy in abnormalities which primarily affect the right side of the heart, or an atypical electrocardiogram showing QS patterns, left anterior hemiblock, deeply inverted septal T inversion, or unusual ST-T changes over the left ventricle.

Histopathologically, 'myocardial dysplasia', indistinguishable on light microscopy from HOCM, is common in many hearts with congenital cardiac lesions, particularly in the ventricular septum. It varies in extent, distribution, and site. Its presence may account for certain unpredictable changes in congenital heart disease.

The influence of 'dysplasia' on the clinical state in both isolated myopathy and when combined with congenital heart lesions depends on its extent and on the occurrence of secondary postnatal haemodynamic and biochemical disturbances. Myocardial dysplasia is probably congenital and common and it may be asymptomatic; pathologist and clinician should be aware of and search for it.

Progress in the management of congenital heart disease has been concerned with early diagnosis of mechanical abnormalities and the successful surgical treatment carried out increasingly earlier in childhood. Attention has been directed to the obvious structural deformity and the resultant circulatory disturbances. This approach has been rewarding but has probably delayed the recognition of coexistent congenital myocardial disease in some patients. When present, this not only can modify the clinical features but also may influence the course after successful surgical correction of the defect.

Now faced with a new medical community, namely the survivors of successful treatment for congenital heart lesions, we are seeing that there is more abnormality in the cardiovascular system than can be treated by the surgeon's skill. There is accumulating evidence (Somerville and Becú, 1977b) that in patients with structural cardiac malformations the congenital abnormality is not always confined to valves, septa, and connections but may also affect the heart muscle, major conducting arteries, and even coronary arteries, and as such are examples of 'congenital cardiovascular disease' (Becú *et al.*, 1976).

Hypertrophic cardiomyopathy in its various forms is obviously a congenital abnormality, often transmitted as a Mendelian dominant (Emanuel *et al.*, 1971), and is a peculiar and bizarre abnormality of the heart muscle. The association of this mysterious disease with structural congenital heart abnormalities now requires reappraisal in the light of current knowledge.

Definition: hypertrophic cardiomyopathy and dysplasia

Damage to the myocardium in fetal life causes various histological changes in the hearts examined after birth, such as fibrosis, infarction, hypertrophy, necrosis, fibroelastosis, and 'dysplasia' in one or both ventricles.

The term 'dysplasia' is used to describe the histological appearance of the myocardium where the muscle fibres are malaligned, disordered,

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truncated, and 'whorled', associated with perinuclear vacuolisation, with such changes located most severely in the ventricular septum. These alterations in myocardial morphology are indistinguishable from those found in the different clinical forms of hypertrophic cardiomyopathy (Ferrans *et al.*, 1972).

Further adaptive pathological changes may develop in the heart during the years after birth as a response to altered function, growth, or as a reparative process. Such changes may result in restoration to, or maintenance of, normal myocardial function or be associated with varying types of clinical ventricular dysfunction. The manifestations of disordered myocardial pathology in the living patient must depend upon whether hypertrophy, fibrosis, or new muscle formation occurs and in what combination, amount, and site.

In living patients, hypertrophic cardiomyopathy presents in different ways, variously described as 'functional obstruction of the left ventricle' (Brock, 1957), asymmetrical septal hypertrophy (ASH) (Teare, 1958), idiopathic hypertrophic subaortic stenosis (IHSS) (Morrow and Braunwald, 1959), hypertrophic obstructive cardiomyopathy (HOCM) (Goodwin *et al.*, 1960), and more recently mid-ventricular HOCM (Falicov and Resnekov, 1977). In all these clinical syndromes the same basic myocardial disorder, namely severe 'dysplasia', is present on histological examination, but this varies in extent, distribution, and severity, accounting for the different clinical presentations. It is interesting that Paré *et al.* (1961) referred to the condition as 'hereditary cardiovascular dysplasia' which to us now appears to be a most appropriate name, showing a correct understanding of the disease. Here the term 'hypertrophic cardiomyopathy' describes the whole group who have the same basic histological disorder of the myocardium, namely 'dysplasia'.

Incidence

Structural congenital heart disease occurs in about 1:100 births if stillborns are included (Mitchell *et al.*, 1971). The incidence of 'isolated' hypertrophic cardiomyopathy in the general population is unknown. The coexistence of clinically obvious hypertrophic cardiomyopathy and congenital cardiac malformations (Somerville and McDonald, 1968; Shem-Tov *et al.*, 1971) appears to be uncommon. When both are recognised in the same patient the myocardial disorder has to be severe to be noticed in the presence of congenital defects which influence the physical signs. Only 19 patients with both conditions have been identified during the past 15 years in the National Heart Hospital. This suggests that the association is rare, below 1 per cent of congenital cardiac lesions seen, and that it might be a coincidence.

Although pathologists have occasionally drawn attention to the abnormal myocardium in congenital heart disease (Berry, 1967; Franciosi and Blanc, 1968), myocardial dysfunction which cannot be explained by the obvious mechanical lesion tends to be ignored or is attributed to damage at the time of operation or to ischaemia in relation to chronic low cardiac output. We believe that if the possibility of congenital abnormalities of heart muscle, particularly dysplasia, were more frequently considered, the incidence of congenital heart disease with hypertrophic cardiomyopathy might be higher.

Recognition depends on criteria for diagnosis as well as awareness of the possibility. Mild cases may be missed particularly if unaware clinicians and pathologists do not search.

Types of congenital cardiac defects associated with hypertrophic cardiomyopathy

When congenital heart disease and hypertrophic cardiomyopathy occur together, the structural lesions reported are usually simple ones, such as secundum atrial septal defect, small ventricular septal defect, persistent ductus, pulmonary valve stenosis, aortic valve stenosis, and coarctation of the aorta. All these as 'isolated' lesions may have a reasonable prognosis which means there may be time for adaptive or reactive myocardial changes to develop.

Hypertrophic cardiomyopathy unassociated with structural abnormalities in the architecture of the heart can cause death in stillborns, newborns, and infants, but clinical manifestations usually appear later after survival has permitted secondary changes to occur in the myocardium. The same appears to be true when hypertrophic cardiomyopathy and congenital heart disease appear in the same patient. Most of the completely documented reports are in children over 5 years and more particularly in adolescents and adults. It must be said that knowledge of myocardial abnormalities particularly 'dysplasia' in infants with complex congenital anomalies is deficient. Observers' eyes are fixed on the gross disorder of cardiac architecture and not on the myocardium. Perhaps study of the myocardium in stillborns and newborns dying with congenital heart disease might reveal interesting information on this. In our experience infarction, fibrosis, and 'dysplasia' do occur in the hearts of infants who die with truncus arteriosus, transposition, and common atrioventricular canal. The clinical contribution of such pathological processes is not yet defined.

Diagnosis of hypertrophic cardiomyopathy in congenital heart disease

Recognition of cardiomyopathy influencing the natural history of congenital heart disease is vital as its presence may spoil the results of surgical treatment as well as leaving an important clinical residuum. When there is added cardiomyopathy of importance the clinical picture does not perfectly fit the textbook description of the basic congenital cardiac anomaly. For example, there may be unpected dyspnoea, heart failure, or cardiomegaly in infancy which improves, or the finding of mitral regurgitation or subaortic stenosis in basically right-sided lesions such as tetralogy of Fallot, atrial septal defect, or pulmonary stenosis provides important clues.

An atypical electrocardiogram appears to be the best guide to the presence of serious additional myocardial disease. Such findings as left anterior hemiblock in a lesion not usually associated with it or extensive and unexpected steep T wave inversion over the left ventricle particularly over septal leads, and QS patterns or the absence of predicted hypertrophy patterns should suggest extensive myocardial dysplasia.

Angiocardiography shows bizarre appearances of the left and sometimes the right ventricular cavity. It is mandatory that in right-sided lesions with any of these unusual features the diagnosis of clinical cardiomyopathy is suspected before invasive investigations are done so that the correct tests and angiocardiograms are performed.

Final confirmation of the diagnosis of hypertrophic cardiomyopathy has tended to rely predominantly upon gross macroscopical appearances at necropsy and the allegedly characteristic histological features of HOCM and ASH. However, we believe that histology and electron microscopy are of value only if the clinical and haemodynamic findings are consistent with the gross appearance of the heart. Indeed, microscopy may be misleading if the more obvious evidence is lacking since 'dysplasia' may be found frequently in congenital heart disease as well as occasionally in the heart muscle in rheumatic heart disease (Dingemans and Becker, 1977).

Problems

Although our studies have shown that dysplastic muscle is common particularly in the cephalad part of the ventricular septum in congenital heart disease we do not know what its contribution is to clinical disease and dysfunction in the living. We doubt if a little dysplasia in the ventricular septum is of importance. Dysplasia perhaps has the potential to influence the haemodynamics and natural history when present in critical amounts or if certain stresses occur. Though dysplastic muscle is also present in the right ventricle in isolated clinical hypertrophic cardiomyopathy this is a disease which mainly affects the left ventricle.

In order to examine the problem of dysplasia and hypertrophic cardiomyopathy in congenital heart disease, the hearts and clinical features of patients with 'isolated' or simple pulmonary valve stenosis were studied since only the right ventricle should be affected by mechanical stresses. Careful sectioning of both ventricles, septa, aorta, and coronary arteries in 25 specimens mainly from infants under the age of 2 years showed that there were large areas of 'dysplastic' myocardium indistinguishable from HOCM, not only in right ventricular muscle but also in the left ventricle and septum, in 25 per cent (Becú *et al.*, 1976). In 5 patients there was obvious severe macroscopical abnormality of the left ventricle and ventricular septum yet no structural valve lesion was present to account for such changes. Retrospective review of the clinical course of dead patients showed that the gross pathological changes in left ventricular myocardium clearly had had clinical effects. The extensive dysplasia in the myocardium must have been congenital since it was also present in some newborns. In another series of living patients treated by pulmonary valvotomy, 15 per cent had suggestive clinical evidence of left ventricular dysfunction and even pulmonary oedema was seen after operation for no obvious reason. One of these patients reinvestigated 8 years later had clinical and angiographic features of hypertrophic myopathy affecting the left ventricle. Routine angiocardiographic investigation of left ventricular function in 39 patients with simple pulmonary valve stenosis has also shown that the left ventricular ejection fraction is unusually high in about 20 per cent and unusually low in 8 out of 10 children under 2 years at the time of operation (Sa'e Melo and Somerville, 1977, unpublished observations).

It is interesting that left ventricular studies in simple pulmonary valve stenosis have been used to establish the normal values for left ventricular function in children (Miller and Swan, 1964). We now believe that this was an unwise choice for normal standards. However, our major difficulty in relating myocardial function to pathological changes is that we do not know the extent of these changes in the ventricular muscle in the living, though study of myocardial biopsy material from the infundibular septum has shown severe dysplasia to be most obvious in those who retain large infundibular gradients after valvotomy.

The aortic media in hearts with pulmonary valve stenosis also showed severe disorientation of the muscular and elastic fibres of the media described as 'higgledy piggledy' arteriopathy and there were frequently lesions in the coronary arteries not related to the severity of myocardial or aortic changes. Such findings surely support the concept of congenital cardiovascular disease which may be present in pulmonary valve stenosis. Indeed, the same aortic changes have also been found in infants and children presenting with systemic hypertension without other congenital heart disease (Becú and Gallo, 1974), in the various congenital syndromes manifesting as supra-aortic stenosis (Somerville and Becú, 1977a), in association with other congenital valve abnormalities including 'thick semilunar valve stenoses' (Somerville and Ross, 1977), and occasionally in patients with isolated hypertrophic cardiomyopathy. It is of note that systolic hypertension may occur with all these lesions, and might be related to conduction of the pulse wave down the abnormal central arteries.

As already stated, the clinical effects of the congenital dysplasia both in the muscle of the heart and in the media of the conducting arteries are really unknown. For the myocardium, the answer probably depends upon the severity and extent of the myocardial dysplasia, necrosis, and fibrosis, and what secondary factors are added. These secondary changes must be influenced by many factors such as stimuli to secondary hypertrophy from a valve obstruction or hypertension, athletic way of life, or altered catecholamine excretion, and all of the above may influence the outcome but are difficult to quantify. Just as in patients with 'isolated' hypertrophic cardiomyopathy the clinical effects are many and different, so are the effects of myocardial dysplasia in congenital heart disease.

Since we now know that many congenitally abnormal hearts contain large areas of dysplastic myocardium, it is justifiable to speculate that this may explain some of the unusual clinical features of survivors with congenital heart disease. For instance, the large left ventricle in small or spontaneously closed ventricular septal defects and the HOCM-like response and disproportionate septal size which may occur with mild bicuspid aortic valve stenosis and with classic congenital aortic valve stenosis in the young, and which is a constant feature of the variant form of aortic valve stenosis with poorly formed lumpy aortic valves and also gross 'higgledy piggledy' changes throughout the aorta (Somerville and Ross, 1977), might be related to the presence of too much dysplastic myocardium. Could the presence of unusual amounts of dysplastic myocardium explain left ventricular dysfunction with secondary mitral cusp prolapse in simple atrial septal defect or the strange septal T inversion which can persist in adolescents with simple congenital heart disease? Perhaps of greater interest is that it might explain the development of subpulmonary obstruction in classic transposition of the great arteries (Somerville and Becú, 1977b) as well as the persistence of infundibular gradients after pulmonary valvotomy for severe pulmonary valve stenosis.

Corroborative evidence, but not proof, comes from the finding of extensive areas of myocardial dysplasia in the appropriate part of the heart in all these situations. We believe that the disturbed circulatory mechanics resulting from the structural lesions stimulates secondary changes in the form and function of the dysplastic muscle so that it in turn influences the mechanical disturbance. Once obstruction in a muscular outflow begins, turbulence occurs, fibrous tissue is laid down, and a vicious circle of effects upon the myocardium may be initiated which is only partly checked by removal of the fixed part of the obstruction. If the primary abnormality is really in the myocardium the clinical state even after good surgery may evolve unfavourably as is shown by the natural history of fixed subaortic stenosis (Somerville and Montoyo, 1971; Somerville and Becú, 1977b). These clinical states share not only the pathological features but also many of the haemodynamic features of the diseases embraced by the term hypertrophic cardiomyopathy. How the dysplastic myocardium actually influences the electrocardiogram also needs clarification.

Aetiological factors

Myocardial dysplasia like the abnormal 'higgledy piggledy' pathology in the aorta with which it is commonly but not constantly associated results from several known different noxious agents which affect the fetus and its cardiovascular system. For instance, both are common in the hearts and vessels of children affected by rubella, and are constant in supra-aortic stenosis of varying causes including vitamin D or vitamin E intoxication, anticonvulsant and other drugs, familial, and even those where there is no obvious cause. Dysplasia or disorganised alignment in cardiovascular tissue probably is the result of incomplete 'healing' or development after intrauterine damage and is probably as non-specific as scar tissue in skin which tells nothing about the original injury. If the concept is true that myocardial dysplasia is frequently present in congenital heart disease as part of diffuse congenital cardiovascular damage caused *in utero,* then it should also be found in other examples of fetal (or congenital) syndromes without obvious structural congenital heart disease. In fact, clinically manifest hypertrophic cardiomyopathy is frequent in Noonan's syndrome (Ehlers *et al.*, 1972), lentiginosis (Somerville and Bonham-Carter, 1972), Friedreich's ataxia (Thorén, 1977), fetal alcohol syndrome (Löser *et al.*, 1977), the children of diabetic mothers (Gutgesell *et al.*, 1976), and other named syndromes (Stocker *et al.*, 1977). It is predicted that the association will be described in more congenital syndromes.

Conclusions

When hypertrophic cardiomyopathy and congenital heart disease coexist the myocardial abnormality must be severe to be recognised. It is likely that the importance and incidence of the association has been underestimated because unaware pathologists and clinicians do not look for it. In the few well-documented cases of the two conditions occurring together the structural congenital cardiac lesion would have had a relatively good prognosis if it had occurred in isolation. This allows time for the post-natal adaptive changes in the abnormal myocardium to occur and influence the clinical presentation. The finding of histological changes called myocardial 'dysplasia', which are indistinguishable from HOCM or ASH, is common in congenital heart defects of all types and may be associated with macroscopical ventricular myocardial abnormalities which cannot be explained by the mechanical disturbance. What determines whether myocardial dysplasia will influence the clinical picture is unknown but we believe it is related to the extent and distribution of abnormal muscle in the heart and the secondary factors which influence it. It is suggested that a number of unusual clinical features in congenital heart disease may be explained by the presence of, and the secondary effects on, excess myocardial dysplasia.

There is a close association between the finding of myocardial dysplasia and abnormal 'higgledy piggledy' changes in the aorta and major conducting arteries, which coexist in some congenital heart diseases, syndromes which manifest with arterial stenoses, and in isolated hypertrophic cardiomyopathy of various aetiologies. We believe that both histological abnormalities are non-specific and are a common end result of an attack on the fetal cardiovascular system.

There is more congenital abnormality in these hearts than the obvious hole, valve abnormality, or disorder of connections, and such hearts should be correctly diagnosed as 'congenital cardiovascular disease'. Both myocardial and arterial disease may affect the survivors with both simple and complex cardiac malformations.

Understanding of this problem may also throw light on the mysterious group of diseases classified as 'hypertrophic cardiomyopathy' which the pathologist can diagnose with apparent certainty when the clinical and macroscopical features are obvious. Our studies suggest that the diagnostic myocardial dysplasia is common in congenital heart disease and may sometimes, depending on the intensity of one's search, be associated with clinical myocardial dysfunction such as is found in hypertrophic cardiomyopathy.

Perhaps there is a parallel between the presence of myocardial dysplasia and that of malignant cells. Many hearts contain myocardial dysplasia, particularly those with structural congenital heart disease since it is a congenital disorder. Similarly, many people have malignant cells but it requires certain secondary factors, predispositions, and critical numbers for them to become a clinical problem. What makes myocardial dysplasia become clinical hypertrophic cardiomyopathy or influence dynamics in congenital heart disease requires more study. The preoccupation with the non-specific histological end point should now be redefined

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Anomalous muscle bundle of the right ventricle
Its recognition and surgical treatment

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SUMMARY This communication presents our experience with 14 cases of congenital heart disease associated with anomalous muscle bundle inside the right ventricular cavity dividing it into two chambers. The clinical picture, natural history, and diagnostic characteristics are described. It can be diagnosed by right ventricular cineangiogram in the anteroposterior position. It can be resected surgically, safely.

Anomalous muscle bundles when found in the right ventricle are generally of little functional significance. On the other hand a muscle bundle situated across the main channel of the right ventricular cavity can, when it becomes hypertrophied, obstruct the circulatory pathway from the tricuspid to pulmonary valve (Fig. 1). The syndrome of anomalous muscle bundle dividing the right ventricle into 2 pressure chambers (2-chambered right ventricle) was first described by Tsifutis *et al.* (1961) and subsequently by various authors (Lucas *et al.*, 1962; Hartmann *et al.*, 1964; Perloff *et al.*, 1965; Hindle *et al.*, 1968; Hartmann *et al.*, 1970; Barnes *et al.*, 1971; Patel and Astley, 1973). This anomalous muscle bundle is quite different from the well-known secondary infundibular hypertrophy occurring in many patients with ventricular septal defect, pulmonary stenosis, and tetralogy of Fallot, though both can occur in the same patient. The anomalous muscle bundle is triangular in shape, with its apex attached to the anterior aspect of the ventricular septum immediately above and in front of the ventricular septal defect. It crosses the right ventricular chamber to insert at the apical portion of the anterior wall of the right ventricle. It is important to recognise this muscle bundle during preoperative assessment, as failure to do so could lead to incomplete repair of the defect or even death of the patient (Patel and Astley, 1973).

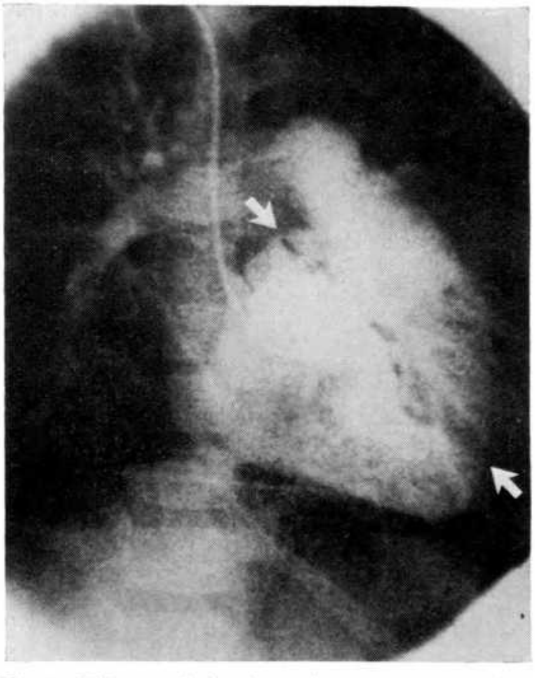

Fig. 1 *Right ventricular cineangiogram, anteroposterior view, showing anomalous muscle bundle dividing the right ventricular cavity into two chambers.*

Subjects and methods

This report describes 14 such cases encountered at the Victoria Hospital, War Memorial Children's Hospital Complex, London, Ontario, from January 1972 to January 1977. Eleven patients have been operated upon successfully with no mortality. Seven have had two or more cardiac catheterisations. In 8 operated cases, the diagnosis was made by cardiac catheterisation (Table 1). The abnormality was not suspected before surgery in the other 3 patients principally because we did not have adequate right ventricular angiograms (Table 2).

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Table 1 *Clinical and haemodynamic data of patients with diagnosis of anomalous muscle bundle (AMB) made during cardiac catheterisation and confirmed by surgery*

Case no.	*Age (y)*	*Procedure*	*Cardiac malformation*	*Pressure gradient across AMB (mmHg)*	Q_p/Q_s	*Angiographic findings*
1	3/12	Cath.	VSD	0	2·8/1	VSD (?) AMB
	5 9/12	Recath.		108	1·1/1	VSD AMB
	5 9/12	Surgery				
	6 11/12	Recath.		11	1/1	Residual AMB
2	4 2/12	Cath.	VSD	65	1·2/1	VSD, AMB
	4 3/12	Surgery				
	5	Recath.		0	1/1	Insignificant VSD
3	6	Cath.	Tetralogy	52	Bidirectional	VSD, AMB, Right aortic arch
	6	Surgery				
	6 10/12	Recath.		20	1/1	Right aortic arch Minimal AMB
4	5 8/12	Cath.	VSD	40	2/1	VSD, AMB
	5 8/12	Surgery				
5	6 1/12	Cath.	VSD	33	1·8/1	VSD, AMB
	6 1/12	Surgery				
6	18 5/12	Cath.	VSD	60	1·8/1	VSD, AMB
	25 5/12	Recath.		72	1·7/1	VSD, AMB
	25 7/12	Surgery				
7	22	Cath.	VSD	65	1·7/1	VSD, AMB
	22	Surgery				
	23	Recath.		15	1·1/1	Small VSD
8	4 8/12	Cath.	Pulm. sten.	0	1/1	Pulm. val. sten., AMB
	4 10/12	Surgery				

Table 2 *Clinical and haemodynamic data of patients with anomalous muscle bundle (AMB) found during surgery*

Case no.	*Age (y)*	*Procedure*	*Cardiac malformation*	*Pressure gradient across AMB (mmHg)*	Q_p/Q_s	*Angiographic findings*
9	4 10/12	Cath.	VSD + AR	26	1·8/1	VSD, AR
	5	Surgery				
10	5 5/12	Cath.	Tetralogy	0	Bidirectional	VSD Pulm. val. + Inf. sten.
	7 11/12	Surgery				
	13 6/12	Recath.		25	2/1	Reopened VSD
	16 4/12	Surgery				
11	7 5/12	Cath.	VSD + AR	26	1·6/1	VSD, AR
	7 5/12	Surgery				

AR, aortic regurgitation.

Table 3 *Clinical and haemodynamic data of patients with anomalous muscle bundle (AMB) diagnosed by angiogram, awaiting surgery*

Case no.	*Age (y)*	*Procedure*	*Cardiac malformation*	*Pressure gradient across AMB (mmHg)*	Q_p/Q_s	*Angiographic findings*
12	4	Cath.	VSD + PS	20	1·2/1	VSD, ASD, PS, AMB
13	6 6/12	Cath.	VSD	0	2·3/1	VSD
	7 6/12	Surgery				
	3 6/12	Recath.		20	1·6/1	Reopened VSD, AMB
14	25	Cath.	VSD	20	1/1	AMB membranous systol aneurysm (VSD spontaneous closure

Three patients in whom the anomalous muscle bundle was diagnosed by cardiac catheterisation and angiography are now waiting for surgical confirmation (Table 3).

Of these 14 cases in the series, 11 were associated with isolated ventricular septal defect, 2 with tetralogy of Fallot, and 1 with pulmonary valve stenosis. The age of discovery of the anomaly, findings at cardiac catheterisation and angiography, and the age at operation in each case are summarised

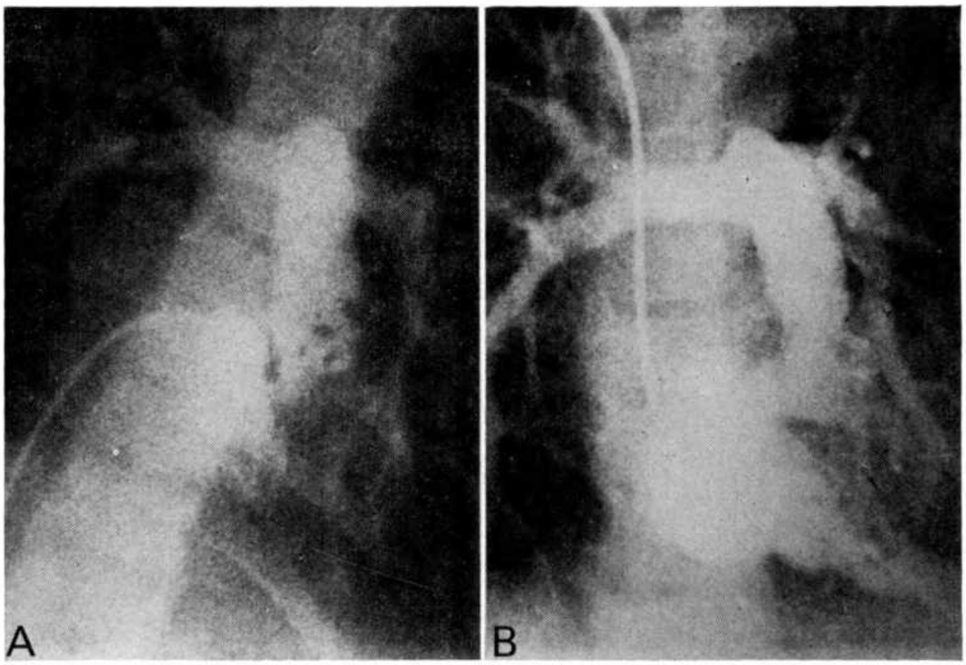

Fig. 2 *Case 1, right ventricular cineangiogram anteroposterior view, showing filling defect in right ventricle, suggests anomalous muscle bundle.* (A) *At 3 months of age;* (B) *at 5 years of age.*

in Tables 1, 2, and 3. Five of the cases are described in more detail.

Case reports

CASE 1

This child, date of birth 20 October 1966, was found to have a heart murmur at 6 weeks of age. The first admission was at 3 months of age for congestive heart failure. He was treated with digitalis. At that time a pansystolic murmur with thrill was noticed at the left lower sternal border with a mid-diastolic murmur at the apex suggesting a large left-to-right shunt at ventricular level. Chest *x*-ray film showed cardiac enlargement with pulmonary plethora. Electrocardiogram showed evidence of left ventricular hypertrophy. Cardiac catheterisation showed a large ventricular septal defect with pulmonary/systemic flow ratio of 2·8:1. There was a systolic pressure gradient of 10 mmHg across the pulmonary outflow tract. Selective right ventricular angiogram showed a shadow in the right ventricular cavity suggesting an anomalous muscle bundle (Fig. 2A). On follow-up examination the congestive heart failure improved. The digitalis was discontinued at 18 months of age.

He was readmitted to the hospital active and well at 5 years of age for recatheterisation (12 July 1972). Examination again revealed a long systolic murmur with thrill located maximally at the second and third left intercostal space slightly lateral to the left sternal border but inside the left midclavicular line. The second sound split widely and moved physiologically. The pulmonary second sound was slightly soft. Chest *x*-ray film showed a normal heart size with prominent main pulmonary artery segment. An electrocardiogram showed combined right and left ventricular hypertrophy. Recatheterisation at this time showed a small ventricular septal defect with pulmonary/systemic flow ratio of 1·1:1. There was a systolic pressure gradient of 110 mmHg across the anomalous muscle bundle. Selective right ventricular angiogram in the anteroposterior position showed a large muscle bundle inside the right ventricle dividing the right ventricle into two parts (Fig. 2B). An aneurysm of the membranous ventricular septum was also noted. He was operated upon at 5 years 9 months of age. The ventricular septal defect was repaired and the anomalous muscle bundle was resected. He was recatheterised 14 months after the operation. No left-to-right shunt was found. The systolic pressure gradient across the anomalous muscle bundle had reduced to 10 mmHg. Right ventricular angiogram

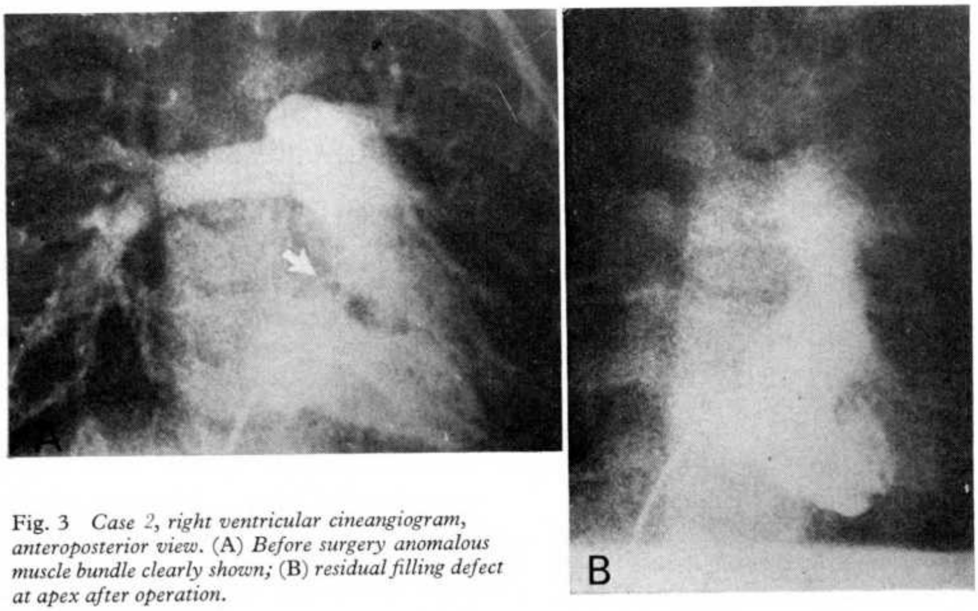

Fig. 3 *Case 2, right ventricular cineangiogram, anteroposterior view.* (A) *Before surgery anomalous muscle bundle clearly shown;* (B) *residual filling defect at apex after operation.*

did show a residual filling defect representing the remains of the muscle bundle.

CASE 2

This boy, date of birth 24 August 1968, had a heart murmur noticed at 2 weeks of age. At that time the clinical diagnosis of ventricular septal defect was made. He became cyanotic at the age of 3. At 4 years 2 months, examination revealed a long systolic murmur at the second and third left intercostal spaces with a soft pulmonary second sound. *X*-ray film showed minimal cardiac enlargement with prominent main pulmonary artery segment. Electrocardiogram showed right atrial hypertrophy and combined ventricular hypertrophy. Cardiac catheterisation was performed on 22 October 1972. A ventricular septal defect with pulmonary/systemic flow ratio of 1·2:1 was found. There was a systolic pressure gradient of 65 mmHg across the mid right ventricular region. Right ventricular angiogram showed a two-chambered right ventricle with a good sized ventricular septal defect (Fig. 3A). He was operated upon at 4 years 3 months of age. He was recatheterised 9 months later. There was no shunt, nor was there any residual pressure gradient within the ventricle. Right ventricular angiogram still showed a minimal filling defect (Fig. 3B).

CASE 3

This boy, date of birth 19 October 1966, was discovered to have a heart murmur at 9 months of age. He became cyanotic at 2 years of age. He was first seen at 5 years of age with the complaint of increasing exercise intolerance. Examination at that time revealed a single second sound. Cardiac catheterisation performed at 6 years of age showed a ventricular septal defect with pulmonary valve stenosis. A right aortic arch was also noted. A systolic pressure gradient of 52 mmHg was noticed across the mid right ventricular region. Right ventricular angiogram showed a normal right ventricular infundibulum with no evidence of infundibulum stenosis. An anomalous muscle bundle was seen inside the right ventricular body. Total correction was performed at the age of 6. Recatheterisation 10 months after operation showed that the systolic pressure gradient across the anomalous muscle bundle had been reduced to 20 mmHg. Right ventricular angiogram did show a minimal residual filling defect with no evidence of a shunt.

CASE 9

This girl, date of birth 19 May 1968, had a ventricular septal defect diagnosed at 3 days of age. Aortic regurgitation became evident on follow-up. She was catheterised at 4 years 10 months of age. On pull-back tracing there was a systolic pressure gradient of 26 mmHg at the mid right ventricular level. Right ventricular angiogram was performed with the tip of the catheter in the distal chamber. A straight line could be seen in the mid right ventricle separating the outflow chamber from the

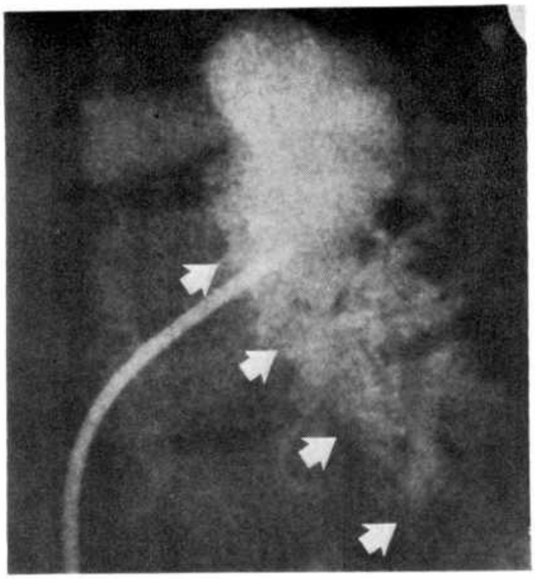

Fig. 4 *Case 9, right ventricular cineangiogram anteroposterior view, with contrast medium injected into the distal chamber. A straight line divides the two chambers signifying the position of the anomalous muscle bundle.*

inflow chamber and signifying the position of the anomalous muscle bundle (Fig. 4). On operation the anomalous muscle bundle was found and was resected. A ventricular septal defect with a pulmonary/systemic flow ratio of 1·8:1 was repaired. Catheterisation has not been repeated.

CASE 11

A girl, date of birth 6 December 1965, had a heart murmur noticed soon after birth and the clinical diagnosis was ventricular septal defect. She remained asymptomatic. At 7½ years of age cardiac catheterisation showed a ventricular septal defect with aortic regurgitation. The pulmonary/systemic flow ratio was 1·6:1. On pull-back tracing there was a systolic pressure gradient of 26 mmHg at mid right ventricular level. Right ventricular angiogram was performed with the patient in the right anterior oblique position. The right ventricular outflow tract was found to be wide open with no significant obstruction. She was operated upon 2 days later. A subpulmonary ventricular septal defect was patched. In mid right ventricle a hypertrophied anomalous muscle bundle was found and resected. This case showed that the anomalous muscle bundle could be seen only with the patient in the anteroposterior position. In the right anterior oblique position or lateral position the anomalous muscle bundle could not be seen clearly.

Discussion

From January 1972 to January 1977 about 600 paediatric patients with significant congenital heart disease were catheterised at the Victoria Hospital, War Memorial Children's Hospital Complex, London, Ontario. Fourteen patients were found to have an anomalous muscle bundle inside the right ventricle. This condition may be more common than previously believed. The anomalous muscle bundle is usually associated with ventricular septal defect. The ventricular septal defect commonly opens into the high pressure proximal chamber. It can also occur in other cardiac malformations that are associated with systolic overloading of the right ventricle as in patients with pulmonary stenosis and tetralogy of Fallot. It is interesting to find that it does not occur in patients with diastolic overload of the right ventricle in atrial septal defect.

All of our patients probably had a ventricular septal defect to start with. Some of them had congestive heart failure in early infancy but improved with time and increasing obstruction by the hypertrophied muscle bundle. We believe that this anomalous muscle bundle is present at birth with no obstruction of the blood flow, but with time and pressure overloading of the right ventricle, the muscle bundle hypertrophies and the pressure gradient increases. This is well illustrated in case 1. Four of our patients had repeated cardiac catheterisation which confirmed that the pressure gradient across the anomalous muscle bundle may increase with time. The degree of obstruction produced may be minimal to severe. The systolic murmur is usually long with an ejection quality and associated with a thrill maximum at the third left intercostal space. The second sound is split widely and moves physiologically with respiration. Chest x-ray film and electrocardiogram are not very helpful in making the diagnosis.

Cardiac catheterisation usually shows a pressure gradient at mid right ventricular level. Often it is difficult to get the tip of the catheter through the opening between the proximal and distal chamber into the right ventricular outflow tract. On pullback tracing the low pressure outflow chamber is excessively long. Catheter manipulation below the pulmonary valve is less likely to cause troublesome extrasystoles and other arrhythmias than in cases of secondary hypertrophy of the right ventricular infundibulum. The diagnosis is best made by right ventricular angiography with the patient in the anteroposterior position. The contrast medium should, however, be injected into the proximal chamber in order to see clearly the anomalous muscle bundle. The anomalous muscle bundle is poorly visualised or may be missed entirely in lateral and left or right anterior oblique views. The anomaly may also be missed if the contrast medium is injected into the distal chamber of the right ventricle. In this event it will be found that the infundibulum is wide open and the discovery of the pressure gradient will be puzzling. However, a straight oblique line running upwards and to the left from the region of the apex should make one suspicious of a dividing bundle between the proximal and distal chamber of the right ventricle which should not be confused with the tricuspid valve.

Surgically, we have found it most convenient to enter the right ventricle below and to the right of the anomalous muscle bundle using a paracoronary incision. In this way the anomalous band is readily identified and can be completely removed. The recognition of the anomalous muscle bundle is extremely important as in its most developed stage it may resemble a ventricular septum with an associated defect. Closure of this opening would, of course, be a catastrophe. After the muscle bundle is completely removed the ventricular septal defect and/or other anomalies are corrected by conventional techniques. After closure of the right ventriculotomy, pressures are taken in both sections of the right ventricle; if there is any significant gradient cardiac pulmonary bypass is reinstituted and the ventriculotomy reopened. The removal of the anomalous muscle bundle of the abnormal band is usually very straightforward provided it is suspected and recognised before the operation.

Of 11 patients operated upon there has been no mortality. Postoperatively there was no major conductive disturbance. We believe that the surgical treatment of patients with an anomalous muscle bundle carries no higher risk than those without the band.

Conclusions

It seems probable that this relatively common condition is present at birth but without significant pressure gradient. With time and pressure overloading of the right ventricle, the muscle bundle may hypertrophy and a pressure gradient develops. Usually the cause of the overload is a ventricular septal defect but other defects can have the same effect. An anomalous muscle bundle can be diagnosed reliably by a good right ventricular angiogram in the anteroposterior position and can be resected surgically safely. It should not be confused with the localised right ventricular infundibular stenosis seen in tetralogy of Fallot.

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Postoperative responses in 'prepared' child after cardiac surgery[1]

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SUMMARY Postoperative reactions of children and adolescents realistically prepared for cardiac surgery were analysed for acute and long-term responses. No cases of delirium or psychoses occurred in the 60 children while they were in hospital. Fifty sets of parents and children answered questionnaires 6 months to 4 years after operation (36 under 1 year, 8 from 1 to 3 years, and 6 over 3 years) and assessment of these showed only one long-term reaction. Evaluation of reactions is presented by age and in detail. The children aged 2 to 7 years had the greatest number of negative reactions and the only long-term reaction also came from this group. Children 8 to 11 years of age had the least number of negative reactions and the highest number of positive gains. Adolescents, 12 to 19 years of age, were often concerned with their body image (wanted to be considered 'well', resented the scar, etc). From the standpoint of emotional stability and after effects, the 8 to 11-year-old group seemed to do best.

The reactions of children to a period in hospital, with or without operative procedures, have been widely reported and analysed (Levy, 1945; Prugh *et al.*, 1953; Robertson, 1958; Bowlby, 1960; Sipowicz and Vernon, 1965; Skipper and Leonard, 1968; Visintainer and Wolfer, 1975). The acute changes in personality while in hospital (depression, withdrawal, and anger) and continuing problems later (phobias, neuroses, and regression) prompted many changes in the handling of the child admitted to hospital. Visiting privileges of the parents were increased, and eventually mothers were allowed to stay in the room with the child. Preparation of the parents and the child was also improved both before and during the hospital stay. The importance of honesty in dealing with a child quickly became apparent. With these changes, the child was more able to cope with the hospital admission and negative reactions decreased. Though the type of operation *per se* did not seem to influence the postoperative reactions in children, there have been more grossly abnormal responses after heart operations in both children and adults, particularly after procedures requiring the heart-lung machine (Edington, 1968; Danilowicz and Gabriel, 1971; Abram, 1973; Kaplan *et al.*, 1974).

Although it is probably idealistic to think that a stay in hospital with or without operation can occur with no adverse reactions, it should continue to be the aim of all physicians to minimise the number and severity of negative responses as well as to encourage those experiences that can be maturing and of positive value. This report assesses the acute and chronic responses in a population of 'prepared' children who were admitted for some form of cardiovascular operation (40 for open heart surgery and 10 for thoracotomy). The realistic method of preparation was chosen over such methods as play therapy and fantasy evaluation because of the nature of the referral service and the limitation of time.

Patients and methods

Sixty patients who had cardiac operations between 1970 and 1975 were studied. Infants were excluded, but otherwise no special selection was used. Of these 60 patients, 50 answered questionnaires relating to their stay in hospital and their postoperative reactions. Essays were written by several of the children and further information was obtained by telephone and by office visits. Because of the mode of referral, the major follow-up had to be accomplished by questionnaire in spite of the recognised drawbacks of this method. Five forms were returned

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Table 1 *Children's reactions to operation: characteristics of patient population (50 patients)*

Sex		*Age (y)*		*Race*	
Male	22	2- 7	26	Black	3
Female	28	8-11	12	White	46
		12-19	12	Oriental	1
Economic status		*Residence*		*Families*	
Low	8	New York City	37	Intact	47
Welfare	3	New York State	13	Divorce	2
Middle	39			Father left	1

Table 2 *Preparation of child for cardiac surgery*

Preoperative: outpatient department

(1) Arrange visit to ward before admission if child not previously admitted to same hospital
(2) Discuss with child and parents hospital stay and operation in general terms; encourage questions and try to decide whether any problems exist
(3) Stress importance of truthfulness to parents regarding preparation; encourage mothers of younger children to make arrangements so they can share a room during admission
(4) With older children, get them to participate in some decisions; do not spring any 'surprises' on them
(5) Involve social service early if any financial, family problems come up

because the family had moved and an additional 5 were not answered.

Apart from excluding gross psychiatric pathology in the children, no specific evaluation of the child's personality was made before the operation. As far as any child with heart disease can be normal, these children seemed to satisfy those criteria (Green and Levitt, 1962; Linde *et al.*, 1971).

Of the 50 who answered, a relatively consistent population emerged, mainly white, middle to upper middle class, and from the metropolitan New York City area (Table 1). All children spoke and understood English. The only communication problems were with the younger children and with 5 patients who had some degree of retardation (a 4-year-old trisomy Down's boy, educable; a 5-year-old Down's translocation mosaic girl with normal IQ and learning disabilities; a 4-year-old girl and a 19-year-old boy with 'brain damage' at birth, both educable; and a 6-year-old trisomy Down's girl functioning at a 3-year level).

Of the 50 families, only 3 were not intact. Two sets of parents were undergoing divorce procedures: the parents of a 2-year-old were still living together, apparently amicably, and the parents of an adolescent girl where the father was out of the house. The third family was that of a black adolescent girl whose father had left the household many years before, lived in Michigan, but continued support to the family.

The 60 patients were examined initially for acute postoperative reactions; no psychosis or delirium was noted in any child. (This is in contrast to an earlier study by Danilowicz and Gabriel (1971) of 68 children, of whom 4 had acute reactions, where preparation of the children was sporadic or nonexistent. However a control series was not studied and comparison with this earlier group is not justified.) In the present group of 60 children, manifestations of anger, dependency, and non-cooperation were noted postoperatively but there were no major somatic reactions and no psychoses or episodes of delirium.

All of the present group of children were prepared in a similar way (Table 2), with most of them having had cardiac catheterisation in the hospital where the operation was to be performed. In cases where this was not true, the parents and child could visit the ward at the time of a preoperative examination or at another prearranged time. The parents were told to be honest with the children and to seek help from the doctor or nurse if questions were asked that they could not deal with. The nursing staff and technicians explained all the procedures at a level appropriate to the age of the child. Older children were involved in the decision regarding the operation as much as possible and the time interval between preparation and operation was kept short (about 2 to 4 weeks) with younger children whose time concepts are limited. Once admitted to the hospital, the children were acquainted with the ward, recovery room, and intensive care unit (Table 3). Procedures and equipment, such as deep breathing (blow bottles and blow toys for younger children and intermittent positive pressure breathing for older children and adolescents), suctioning, intravenous lines, urinary catheters, face masks, oxygen tents, and monitoring devices, were shown and described to the children before the operation. One of the authors was closely involved with the preparation and assessed its adequacy. The parents and children were considered 'well prepared' and, of the 50 answers received, 49 parents agreed with this evaluation. One set of parents felt the child was well prepared but that their responsibilities about

Table 3 *Preparation of child for cardiac surgery*

Preoperative preparation: in hospital

(1) Show child and parents ward routines; show intensive care unit (oxygen masks, tents, monitoring devices, etc.)
(2) Discuss at level appropriate for age details of postoperative period; provide time for questions; with older children and adolescents, a time for questions away from parents is often appreciated
(3) Explain all procedures (what and why) before doing them
(4) Arrange for demonstration of respiratory therapy (blow bottles and blow toys for younger children; IPPB for older children); stress importance of this to earlier discharge and fewer complications

Table 4 *Preparation of child for cardiac surgery*

Postoperative preparation: in hospital
(1) Encourage and support parents in staying with child as needed
(2) Continue to explain all procedures
(3) Encourage child to talk it out and offer proper support; once child is ambulatory on ward, 'play-therapy' and 'acting out the operation' can be useful
(4) Try to keep stress on parents to a minimum; panic in parents is quickly conveyed to child (information about occurrence of low grade fever, pulmonary secretions, wound pain, when given ahead of time makes these incidents much less threatening when they occur)

visiting and care to the child after operation were not explained in enough detail to make them feel comfortable. Mothers usually shared a room with the younger children and some member of the family was present for most if not all of the day. Parents were told to be present before the child went to the operating room and again when the child awoke in the recovery room after the operation (Table 4). The recovery room visiting time was limited, but luckily most children (42/50) spent only 4 to 12 hours there (Table 5). In the intensive care unit, the visiting time was open only to the parents (exceptions were made as indicated by the family constellation), but there was no time limitation and mothers could stay at the bedside as long as they wished. Time in the intensive care unit was also usually short (1 to 3 days, Table 5) though 2 children stayed much longer. At the time of discharge from hospital, the parents were told to expect some changes in behaviour of the children for a time. They were reassured that these changes were usually normal and were told to call if any problems arose (Table 6). Some leniency was encouraged but lack of discipline was not. The questionnaires were sent out no earlier than 3 months after the operation so that continuing reactions would be identified. If reactions were still present at the time of the return of the questionnaire, further assessment was undertaken.

Analysis of parent's and children's initial responses (Table 7)

Table 5 *Hospital time of patient population*

Days in RR	*No.*	*Days in ICU*	*No.*	*Days on ward*	*No.*
Under 1	36	1	8	10	30
1-2	12	2	32	10-14	16
2-7	1	3	6	14-21	2
Over 7	1	4-7	3	Over 21	2
		Over 7	1		

RR, recovery room; ICU, intensive care unit.

Table 6 *Preparation of child for cardiac surgery*

Postoperative instructions at discharge
(1) Prepare parents for some personality changes, regressive behaviour; tell them to allow for some of this but not to drop discipline completely
(2) Get child to return to as normal activity as physically possible; try to allay anxieties about incision to both child and parents
(3) Ensure easy access by phone and/or clinic visit as needed
(4) Make sure school has all needed information about older child so that return is facilitated

Parents were almost unanimous in stating that the waiting during the child's operation was the worst part of the stay in hospital (39/44; 6 sets of parents did not reply to this question). For others, the worst time was seeing the child in the recovery room (4) and having the child return to the operating room for bleeding (1). For the 26 children aged 2 to 7 years, the worst portions were reported as follows: needles (12), suctioning (4), separation from parents (4), intensive care unit/recovery room (3), apprehension (2), and disappointment with the

Table 7 *Postoperative reactions*

Reactions	*2-7 years (n = 26)*	*8-11 years (n = 12)*	*12-19 years (n = 12)*
Immediate postoperative delirium/psychosis	0	0	0
What was worst? (immediate)			
Needles	12	3	0
Suctioning	4	0	0
Separation	5	0	0
ICU/RR	3	0	3
Apprehension/anxiety	2	3	4
Pain	0	2	4
'Hospital food'	0	0	1
Not answered	—	4	—
Discussion of operation?			
Yes	26	12	9
No	—	—	2
±	—	—	1
Reaction to scar			
Showed off; proud of it	16	6	0
Disliked	3	2	3
No mention made	7	4	9
Positive responses	9	12	6
More sure of self	0	6	2
Better grades, concentration	3	1	2
More mature	5	3	2
Less afraid of doctor	2	2	0
Loss of enuresis	1	2	—
Physical improvement	14	9	8
Negative responses	26	2	9
Withdrawn	0	1	4
Seeking praise, notice	0	0	3
Resentful of parents	2	0	2
Sleep disturbances	13	1	0
Bedwetting	3	0	0
Apprehensive, fearful	10	0	0
Demanding of parents	10	0	0
Regressive behaviour	13	0	0
Long term reactions	1 (1 year)	0	0

operative result (1). In this age group, parental interpretation often blended with or overshadowed the responses of the children. In the very young children, the parental responses replaced the children's responses in some instances. For the 12 children who were between 8 and 11 years old, the worst part was reported as follows: needles (3), anxiety/apprehension (4), intensive care unit/recovery room (3), and pain (2). For the patients aged 12 to 19 years, the worst part was pain (4), anxiety/apprehension (4), intensive care unit/recovery room (3), and 'hospital food' (1). Fear of physical threat and separation was more prominent in the youngest group while apprehension and physical pain seemed more prominent in the older groups.

Analysis of responses after discharge (Table 7)

Talking about the operation and stay in hospital was a common finding in and out of the hospital and was present in all age groups (Danilowicz and Gabriel, 1976). With the younger children (2 to 7 and 8 to 11 years), open and free discussion was invariable, with 22 of the 38 children being proud of and showing off the scar. Five children in these younger groups disliked the scar while others made no special reference to it. In the adolescent group, the scar was disliked by 3 and ignored by 9. Open discussion was absent in 3 adolescents, 2 girls refusing to talk about the operation at all and 1 boy being reticent about the topic. One adolescent, a 16-year-old black girl, on the other hand, was very introspective and communicative; she subsequently sent a long poem that she had written about her illness and operation to her cardiologist and surgeon (Danilowicz and Gabriel, 1976).

From the answers received to the questionnaires, we were able to place the reactions into a negative and positive group. A response was considered negative if it interfered with the child's normal life (for example fear of white coats, withdrawn and frightened, overdemanding of parents with fear of strangers, etc.) or caused a disruption of previously normal behaviour patterns (for example sleep disturbances such as nightmares or night terrors, regressive behaviour such as bedwetting, bottle feeding, baby talk, or clinging behaviour). Positive responses were divided into two categories. In one was the direct physical improvement seen in children who were symptomatic before the operation (better exercise tolerance, better weight gain, fewer infections). Though physical improvement may have contributed to the other positive gains, this aspect was not used in the comparison since it was not specific for any group. The second category of positive reponses included those aspects of maturing behaviour which occurred in spite of (or perhaps because of) the stay in hospital. For example, parents mentioned that the children were more sure of themselves, related to their doctors better, were doing better socially and intellectually in school, stopped bed wetting, etc. The incidence of negative and positive reactions in the 3 age groups was compared using the χ^2 fourfold table.

Although negative responses were expected and elicited in all groups, the infrequency of negative responses in the 8 to 11-year-olds (2/12) was impressive compared with the 2 to 7-year-olds ($\chi^2 = 17$; $P < 0{\cdot}01$), and compared with the 12 to 19-year-olds ($\chi^2 = 14{\cdot}2$; $P < 0{\cdot}01$). All 26 of the 2 to 7-year-old group had some negative reactions as did 9/12 of the adolescents. Positive responses (other than physical improvement) were reported in all age groups, but again the middle age group stood out with all 12 reporting positive responses (even in the 2 where negative responses were also noted), compared with the 2 to 7-year-olds ($\chi^2 = 19{\cdot}4$; $P < 0{\cdot}01$), and compared with the adolescents ($\chi^2 = 5{\cdot}5$; $P < 0{\cdot}01$). Nine of the 26 youngest children had some positive responses reported as did 6 of the 12 adolescents. Though these occur in children as a result of the natural process of maturing, their occurrence during a stay in hospital shows that even this experience can be integrated into the maturing process. From our observations, the middle group seems most likely to cope with a stay in hospital in this manner.

Of the negative reactions, most had disappeared by 1 to 2 months after operation. Sleep disturbances (seen in half of the 2 to 7-year-old group) included night terrors, nightmares, difficulty in falling asleep without a parent in the room, wishing to sleep with the parents, return to the need for a security object or light, and restless sleep. These subsided by 1 to 2 weeks after discharge, though 1 child continued to have nightmares for 1 month. This happened in a 4-year-old girl whose stay in hospital was prolonged to 8 weeks, 2 weeks of which were spent on a respirator with a tracheostomy. She was also the only child with a long-term reaction (1 year). After discharge, this child regressed to the bottle and used baby talk again. She refused to stay with baby sitters (no problem before operation) and demanded full attention from her mother. Night terrors went on for 2 weeks with nightmares and restless sleep for an additional 2 weeks. About 6 months after operation the child's physical condition was noticeably improved from her preoperative state and with this the girl began to regain her independence. She subsequently made excellent gains in learning and by 18 months after operation she began to talk proudly about her operation, how her heart was fixed, and how well she was doing because of the operation ('delayed discussion'). Her subsequent entry into school was no problem and she continued to do well. In contrast to this child, the 6-year-old boy who had to remain in hospital for 6 weeks for treatment of bacterial endocarditis (Danilowicz *et al.*, 1974) had only minor sleep disturbances for the first week after discharge. However, he was never critically ill and his major problem was that of an intravenous line for 4 weeks. This did not stop him from walking; he was able to attend school, go to the playroom, and take part in scheduled ward activities. This boy, therefore, had little of the isolation that the 4-year-old girl had to endure and he did not sustain nearly as much physical trauma.

Discussion

Over the past 40 years, there has been a growing awareness among all physicians of the needs of children who must stay in the hospital for greater or lesser periods of time. The major problems associated with hospital stay for the child and adolescent are those of a dependent individual separated from parents and of physical trauma (pain, coercion) at an age when ability to deal with these situations is still limited. While the issue of parental loss has been handled by more flexible visiting procedures, the problem of physical trauma with its short and long term sequelae is more difficult. Though many surgical procedures can be dealt with by short stays in hospital, more complex ones such as cardiac operations require longer admissions, with all the attendant emotional problems.

It is obvious that medicine, apart from adequate analgesia, can do little to modify the truly painful, invasive, and assaulting qualities of major surgery. In fact, after cardiac operations, the patient is called upon to cough and breathe deeply in spite of the pain incurred as well as to co-operate with very frightening procedures such as suctioning. Our efforts to prepare children and adolescents adequately for such experiences were rewarded in this group by the absence of grossly abnormal acute reactions as well as relatively short-lived 'chronic' responses. While a realistically prepared child is told what to expect, it is important to reinforce the information before actually carrying out a procedure. After the operation, there appears to be a need for the children to integrate all the experiences over a longer period of time. The children apparently accomplish this using two major mechanisms. The first is through a period of regressive dependent behaviour which is then followed by the second, a longer period of 'working through' by showing off the scar and talking about the operation and stay in hospital. This type of behavioural response has been previously described by Anna Freud (1946) and Robertson (1958).

There do appear to be several factors which may impair the total adjustment process. A repressing, denying attitude by the parents in the early postoperative period may slow adjustment by not allowing adequate discussion and working out of emotional involvements. The presence of another individual who can help the child (for example the play therapist) is useful in these instances. The other more difficult problem is that of the medical complication which prolongs convalescence. The stresses of medical complications put both the child and the family at greater risk and demand much more support from the doctors and staff.

Some recognition must be given to the special problems of the normal adolescent, which are related to the difficulties experienced by this age group (Blos, 1962; Erikson, 1963). While the events surrounding and subsequent to surgery appear to be handled in the same way as in the younger children, there may be a greater withdrawal by the adolescent, who is more interested in independence and becomes resistant to outside authority. Concern about body image is seen in the adolescent's anxiety about scarring and disfigurement. Sexual identity and attractiveness are a preoccupation of the normal adolescent and may add to the problems that arise during the stay in hospital. The 'working through' may be a more prolonged process in this age group.

Conclusions

The responses in children realistically prepared for their operation seem relatively mild and rarely last beyond one month after discharge. Prolonged reactions may occur in children having a complicated and medically difficult postoperative course, particularly if significant parental separation or verbal isolation occurs in a younger child. Although the numbers are small, the responses of the 8 to 11-year-old group are significantly better and suggest that, if a choice of time is possible, this age may be a better time for elective surgery. Adolescents and the 2 to 7-year-old children cope with the threat to mind and body less well and are more prone to negative reactions even with adequate preparation. There seems to be no preparation that can totally protect the child who develops severe complications with a resultant prolonged stay in hospital and multiple manipulations. Support of both the child and the parents is important when this occurs. Postoperative discussion and working-through appear to be essential mechanisms used by children to integrate and deal with the total experience of surgery and hospital admission. Any environment that makes it easier for the child to work this out (puppet play, play acting, school show and tell, co-operative and tolerant parents) will probably contribute to an earlier integration and an earlier return to normal activities.

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Case reports

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Aortic regurgitation as a manifestation of giant cell arteritis

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SUMMARY The detailed clinical findings of a 65-year-old woman who developed aortic regurgitation caused by giant cell aortitis are presented. The initial phase of the disease was dominated by severe non-specific constitutional symptomatology suggesting infective endocarditis or a malignancy. Aortic regurgitation as a manifestation of giant cell arteritis has hitherto received scant attention in the published reports. The clinical and therapeutic relevance of this masquerade is discussed.

Although it has long been established that giant cell arteritis is a generalised vascular disease (Gilmour, 1941; Cooke *et al.*, 1946), major involvement of the aorta or its branches has been poorly recognised by clinicians (Klein *et al.*, 1975). In this paper, we wish to draw attention to the occurrence of aortic regurgitation as a manifestation of giant cell aortitis and to discuss the therapeutic importance of recognising this association.

Case report

The patient, a 65-year-old white woman, was first seen by one of the authors in March 1972. She had been admitted to a surgical ward a few weeks earlier having been unwell for 5 months, with increasing tiredness, anorexia, a gradual loss of 19 kg in weight and fairly constant aching discomfort in the central abdomen and right iliac fossa. In 1965 and 1971 a urethral carbuncle had required treatment by diathermy and during this period recurrent frequency of micturition had proved repeatedly to be caused by infection with *Esch. coli.* On this occasion though intermittent mild fever was noted, urine cultures, blood urea, and an intravenous pyelogram were all normal. The erythrocyte sedimentation rate (ESR), however, was repeatedly over 100 mm in the first hour and the haemoglobin level persistently low at 9·7 g/dl (66%). The peripheral blood film showed only mild anisocytosis and occasional hypochromasia with normal white cell morphology and distribution.

Physical examination was unhelpful, there being no definite abnormality in the abdomen and no clinical features suggesting myelomatosis or leukaemia. The blood pressure was 130/80 mmHg and there were no cardiac murmurs. The temporal arteries were easily located, being non-tender and pulsatile. No bruits were heard over the neck or abdomen. Chest *x*-ray film, studies of liver function, tests for faecal occult blood, cholecystogram, blood cultures, barium meal, sternal marrow aspirate, electrocardiogram, and cultures of urine and sputum for tubercle bacilli all showed no abnormality. A barium enema disclosed no lesions other than mild diverticular disease. The serum iron level was low at 40 μg/100 ml (7·1 μmol/1), but stainable iron was present in the marrow smears. Serum protein electrophoresis showed a diffusely increased gammaglobulin of 1·93 g/100 ml and a search for Bence Jones protein was negative. Her Wassermann reaction and tests for rheumatoid factor and lupus erythematosus cells were negative. Red cells were identified on urinary microscopy on several occasions.

Since she remained unwell a month after admission to hospital, with persistence of pronounced anaemia and gross rise in the ESR, a laparotomy was carried out but no abnormality was shown. She was transferred to the medical unit where further observation and studies failed to establish a diagnosis. She was finally discharged nearly a month later, there having been moderate improvement

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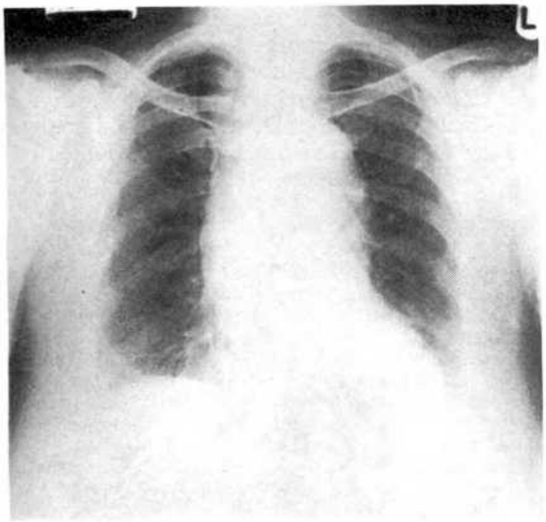

Fig. 1 *Chest* x-*ray film showing dilatation of aorta.*

with no specific treatment. At that time the haemoglobin was 11·0 g/dl (75%), the ESR 6 mm in the first hour, and her weight was 70·7 kg. Five months later she had gained 12·7 kg in weight, though she was still tired. The ESR was 8 mm in the first hour and the haemoglobin 13·7 g/dl (94%).

Two years later in 1974 she was again seen complaining of tiredness, unpleasant throbbing in the neck, and intermittent heavy retrosternal discomfort. Her weight had risen further to 90·7 kg, the ESR being normal and the haemoglobin 14·1 g/dl (97%). There was now, however, a grade 2/6 midsystolic murmur at the base and an immediate soft diastolic murmur at the left sternal edge, indicating mild aortic regurgitation. The blood pressure was 160/85 mmHg and chest film showed dilatation of the aorta (Fig. 1). The temporal arteries still appeared normal to clinical examination, but biopsy of the right artery confirmed a diagnosis of giant cell arteritis. *X*-ray films of the spine and sacroiliac joints showed only minor osteoarthritic changes. Observation over the next 5 months showed a fall of 12·7 kg in weight and suggested that, despite the normal ESR, the aortic regurgitation was increasing in severity. She continued to complain of aching discomfort in the front and back of the chest and an archaortogram was carried out to assess the severity and extent of the aortic disease. This showed distinct dilatation of the whole of the thoracic aorta and its branches (Fig. 2). Treatment with prednisolone 3 mg t.d.s. was initiated and within a few weeks she reported clearing of the fatigue and the pains in the chest which had troubled her for over a year. At the last assessment in December 1976 she remained well and there were neither clinical nor electrocardiographic features to suggest deterioration of the aortic regurgitation.

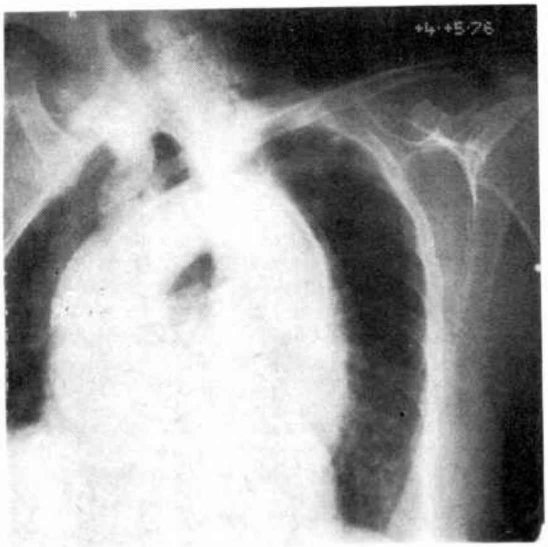

Fig. 2 *Aortogram showing dilatation of the whole of the thoracic aorta and its branches.*

Discussion

Giant cell arteritis which primarily affects elderly patients is not a rare disease but the many guises under which it may present is undoubtedly the major factor responsible for diagnostic failures (Paulley and Hughes 1960; Hamilton *et al.*, 1971). In addition, Paulley and Hughes (1960) have emphasised that, 'in remission it may only sleep' and 'if untreated it may progress slowly leading to serious complications or sometimes more rapidly to a fatal termination'. The combination of anaemia, weight loss, and rapid ESR in the elderly raises apprehensions of occult malignancy, and, as in the present case, the patient is often subjected fruitlessly to a wide range of investigations including exploratory laparotomy. Despite our interest in the various arteritic syndromes (Strachan, 1964, 1966) it was more than two years after the initial presentation that the finding of aortic regurgitation prompted the diagnosis of an underlying giant cell arteritis. Though the temporal arteries were 'normal' clinically, the histological features on biopsy were typical of active giant cell arteritis, emphasising the importance of the asymptomatic temporal artery as a source of histological and arteriographical confirmation of the diagnosis in possible cases (Gillanders *et al.*, 1969; Bonventre, 1974). Unfortunately, there is still great reluctance on the part of clinicians to undertake these investigations in the absence of tenderness or pulselessness of a temporal artery.

Aortic regurgitation as a manifestation of giant cell arteritis has received very scant attention (Paulley and Hughes, 1960; Austen and Blennerhassett, 1965; Castleman and McNeely, 1967, 1971). Textbooks of cardiology and comprehensive reviews (Roberts *et al.*, 1973) list extremely rare and untreatable causes of aortic regurgitation but fail to mention giant cell arteritis. It is, therefore, not surprising that this association may be completely overlooked during life resulting in years of ill health with confirmation of the diagnosis occurring only at necropsy (Castleman and McNeely, 1971). It probably occurs more frequently than previously suspected, accounting for some of the cases of 'negative culture' endocarditis. Fauchald *et al.* (1972) found 3 instances of aortic regurgitation in the course of observing 35 biopsy proven cases of giant cell arteritis, though these authors did not present any clinical data.

The pathogenesis of the aortic regurgitation is probably dilatation of the aortic valve ring but necropsy reports are very limited (Castleman and McNeely, 1971). The radiological finding of pronounced dilatation of the ascending aorta in our patient suggests that a similar mechanism is responsible for the aortic regurgitation. Consequently, in patients with suspected or proven giant cell arteritis, careful and regular auscultation is recommended to identify not only vascular bruits but also the aortic regurgitant murmur.

The recognition of aortic involvement as a manifestation of giant cell arteritis has therapeutic implications. Early diagnosis and treatment with corticosteroids may prevent aortic rupture and death or occlusions of its major branches (Klein *et al.*, 1975). Ill-defined constitutional symptoms in association with established or developing aortic regurgitation may, despite negative blood cultures, be interpreted as indicating infective endocarditis and the patient may be subjected to at least 6 weeks of intensive antibiotic therapy (Oakley, 1974). Moreover, delay or failure to reach the correct diagnosis leaves the patient at great risk of developing serious complications, such as blindness and stroke.

The present case, together with the limited number of previous reports, emphasize that the possibility of giant cell arteritis should be entertained in patients presenting with vague symptoms and aortic regurgitation. The latter manifestation is a facet of the disease which is of undoubted relevance to the cardiologist.

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British Heart Journal, 1978, **40**, 1055-1058

Cardiac and respiratory standstill during sleep

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SUMMARY An obese man, with an attack of myocardial ischaemia, developed arrhythmias only when he was asleep. Episodes of sinus bradycardia occurred progressing to atrioventricular block and sinus arrest. These changes in the cardiac rhythm coincided with periods of sleep apnoea.

We describe a patient with myocardial ischaemia who had both cardiac and respiratory arrhythmias during sleep.

Case report

The patient, a 47-year-old train driver, was admitted to the coronary care unit at 0500 hours. He had been awakened from sleep with sweating, nausea, and a severe chest tightness, which had lasted for 2 hours.

The patient was obese. He was in sinus rhythm and there were no abnormal cardiac signs. The blood pressure was 170/110 mmHg and remained high. The electrocardiogram, initially normal, later developed T wave inversion in leads I, aVL, V5, and V6. Serum levels of the cardiac enzymes remained normal, and an attack of myocardial ischaemia was diagnosed. No further episodes of pain occurred during his hospital stay and the only complications were the respiratory and cardiac arrhythmias described below. He was never given any digitalis, diuretic, or hypnotic drugs.

RESPIRATORY AND CARDIAC ARRHYTHMIAS

After admission the patient slept for a short period. During this sleep it was noticed that his respiratory pattern became irregular, with long periods of apnoea interrupted by short spells of snorting breaths. In the apnoeic periods his heart rate progressively slowed reaching as low as 18/min, and the PR interval lengthened to 0·49 s. During the longer apnoeic pauses complete atrioventricular block and then sinus arrest occurred, with slow idioventricular escape beats. When he was wakened the respiration and cardiac rhythm immediately became normal. The electrocardiogram and ventilation abnormalities reappeared at intervals during further episodes of sleep that day and night.

The respiratory and cardiac arrhythmias are illustrated in the Figure. Since all effective breaths produced snorting noises the respiratory pattern was recorded using a phonocardiogram microphone taped lightly over the larynx. As sleep deepened over 10 to 20 minutes the respiratory rhythm became irregular with progressively longer apnoeic periods. No chest or abdominal movements were seen until the end of an interval of apnoea when, for a few seconds, very small and ineffective movements of the chest occurred, followed by the abrupt onset of noisy, deep respirations. During 9 consecutive respiratory cycles the apnoeic period averaged 63 seconds (range 27–83 s) and the period of noisy breathing averaged 10·5 seconds (range 9–14 s).

Arterial blood samples from a Medicut catheter in a radial artery were taken at the beginning and end of apnoeic periods. The results of the arterial blood gas analysis are given in the Table.

By the 4th day after admission the respiratory arrhythmia persisted but only a sinus bradycardia occurred during apnoea.

ELECTROENCEPHALOGRAM

An electroencephalogram was recorded during sleep and showed the abrupt onset of an arousal pattern 2 to 3 seconds before the end of an apnoea, indicating that the patient had to wake himself up in order to breath adequately.

LUNG FUNCTION STUDIES

The chest *x*-ray, FEV_1, FVC, and CO transfer factor were normal. Arterial blood samples taken with the patient asleep, awake, and after hyperventilation had Po_2 levels of 5·1, 8·8, and 11·7 kPa, respectively, showing that some hypoventilation was present during wakefulness as well as in sleep. CO_2 rebreathing response and breathholding time were normal. The ear, nose, and throat examination disclosed slight septal deviation but the upper air-

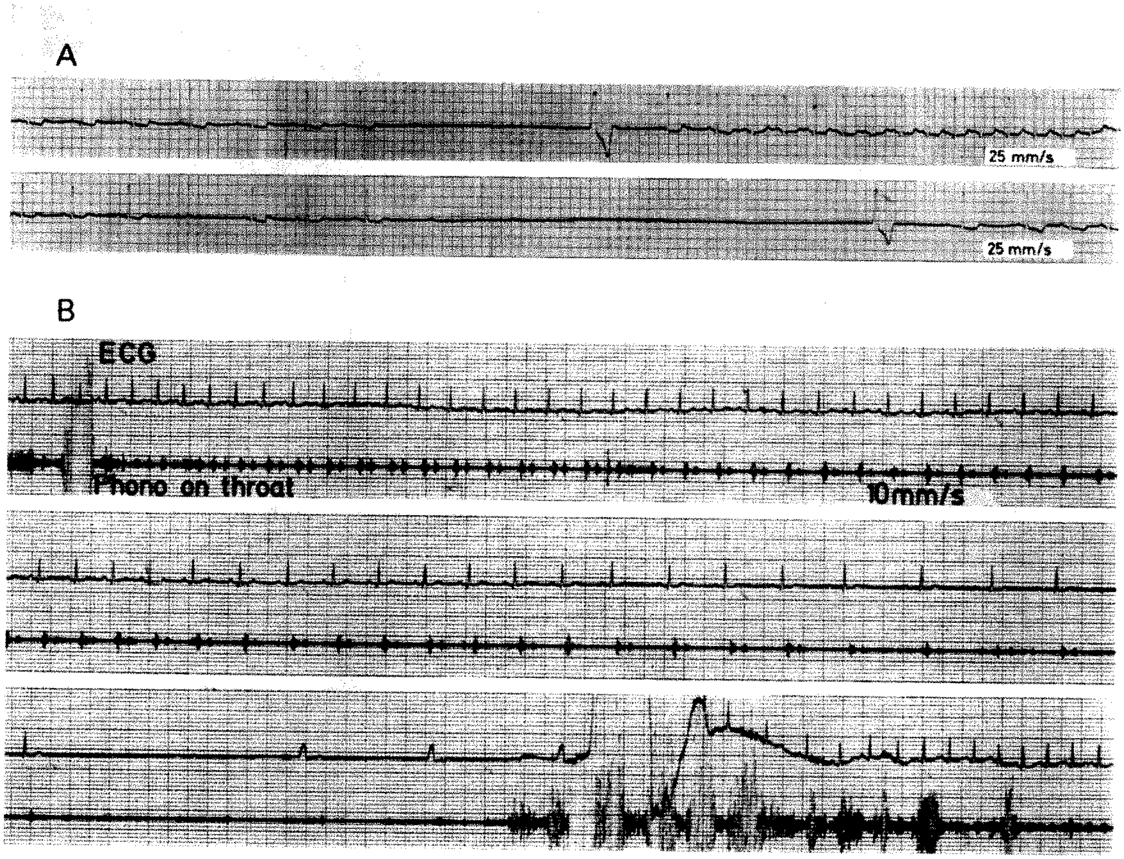

Fig. *(A) Cardiac arrhythmias recorded at the end of two periods of prolonged sleep apnoea; (B) simultaneous recordings (10 mm/s) of the electrocardiogram and the respiratory pattern. All effective breaths produced snoring sounds and were recorded with a microphone on the throat. The strips are continuous.*

Table *Changes in 3 paired sets of arterial blood samples taken at the beginning and end of apnoeic periods during sleep*

	Beginning of apnoea	*End of apnoea*
P_{O_2} (kPa)	6·8, 7·0, 6·1	6·4, 6·9, 5·3
(normal range 12·6–13·3)	mean 6·6	mean 6·2
P_{CO_2} (kPa)	5·7, 5·6, 5·9	6·7, 6·7, 6·5
(normal range 4·5–6·0)	mean 5·7	mean 6·6
H^+ concentration (nmol/l)	39, 41, 41	42, 45, 45
(normal range 45–38)	mean 40	mean 44
	(*p*H 7·40)	(*p*H 7·36)

Conversion factor; 1 kPa ≈ 7·5 mmHg.

ways were considered adequate and palatal closure was complete.

OBESITY

Although tall (187 cm) and broad the patient was considerably obese. He weighed 138 kg and, as assessed from the Desirable Weight tables of the Metropolitan Life Insurance Company, he was 48 kg overweight. His total body water, measured by hydrogen isotope, was 60·4 litres; in a normal person this would correspond to a body weight of 102 kg, indicating his excessive weight was 36 kg (Widdowson and Dickerson, 1964).

PAST HISTORY OF SLEEP DISORDER

The patient's wife had been 'too well aware' of the patient's noisy, irregular breathing during sleep. She said that the abnormal pattern had started immediately after an attack of 'severe glandular fever' eight years earlier. During this illness the patient had been feverish and for a few days had been confused and delirious. Since this illness he had tended to fall asleep at inappropriate times. While sitting at a table during a meal he could fall asleep with food still in his mouth. He stated that he often found sleep was not satisfying and he still felt tired each morning.

PROGRESS

The patient was put on a weight reducing diet and supervised at regular follow-up visits. Six months after admission he had lost 27 kg. He had no cardiac symptoms and reported feeling very much fitter and alert. He now enjoyed his sleep and his wife expressed her delight at his quieter and less restless nights. He was readmitted for overnight observation six months after his first admission. The respiratory pattern during sleep still showed some irregularity, varying between very small and very deep respiratory movements but the overall ventilation was considerably improved. There were no periods of total apnoea and intervals of small amplitude chest movements never lasted beyond 10 seconds. Heart rate varied in a cyclical fashion between 60 and 42 beats per minute. There was no change in the PR interval and no sinoatrial arrest. During deep sleep Po_2 was 10·2 kPa (95·5% saturation), while awake 11·4 kPa (97·7%), and after hyperventilation at 15·69 kPa (98·8%): Pco_2 was 5·18, 5·05, and 3·06 kPa, respectively.

Discussion

Our patient suffered from periods of 'sleep apnoea'. This is an uncommon but distinctive form of sleep disturbance first described by Gastaut *et al.* (1965). This type of periodic breathing is associated with the Pickwickian syndrome and other hypersomnias, but can also occur in otherwise normal non-obese persons who complain of poor sleeping (Guilleminault *et al.*, 1975a). The features and pathogenesis of sleep apnoea have recently been reviewed by Guilleminault *et al.* (1976).

This patient's distinct obesity, daytime somnolence, and periodic breathing are features of the Pickwickian syndrome (Burwell *et al.*, 1956), but he did not have the characteristic polycythaemia, cor pulmonale, or the abnormal response to inhaled carbon dioxide. The distinct improvement after weight reduction indicates that his obesity was an important factor. However, the persistence of a milder respiratory abnormality in sleep after weight loss suggests that an additional central nervous system abnormality was also present. The sudden start to his disturbed sleep after his confusional state raises the possibility that he may have had an attack of encephalitis which damaged the brainstem centres. A past history of encephalitis has been found in some cases of chronic hypoventilation (Fishman, 1972).

The cardiac arrhythmia was produced by the conjunction of two factors: the attack of myocardial ischaemia and the hypoxia during sleep apnoea. On admission it always coincided with the onset of sleep apnoea but disappeared after a few days, though the respiratory abnormality persisted. After the acute phase of the ischaemia he continued to show some fluctuation in heart rate during the respiratory cycles in sleep, with a slower sinus rate during apnoea. A vicious cycle is likely to have been created with a falling heart rate and worsening hypoxia increasingly compromising already ischaemic sinoatrial and atrioventricular nodes. Kryger *et al.* (1974) described a patient with sleep apnoea who had transient bouts of atrial fibrillation during apnoea. Tilkian *et al.* (1975) recorded sinus and ventricular arrest and ventricular tachycardia in patients with sleep apnoea.

This case shows that coronary heart disease may combine with sleep apnoea to produce a major arrhythmia. Such arrhythmias may be one cause of the not infrequent sudden deaths in patients with the Pickwickian syndrome (MacGregor *et al.*, 1970). Sleep apnoea has also been postulated as a possible cause of cot deaths (Guilleminault *et al.*, 1975b). Sleep apnoea should be suspected when there is a history of unsatisfying, restless sleep interrupted by bouts of snoring or in any patient with a hypersomnia syndrome. Hypnotic and sedative drugs should be avoided in these cases since they may precipitate a respiratory crisis which can be fatal (Hishikawa *et al.*, 1972; Guilleminault *et al.*, 1975a). Weight loss is the best treatment but occasional cases require tracheostomy (Kryger *et al.*, 1974, Coccagna *et al.*, 1972) which has an immediate effect in correcting the respiratory and cardiac abnormalities.

We thank Dr G. J. R. McHardy, Dr H. R. A. Townsend, and Dr R. H. Smith for their help and advice.

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Requests for reprints to Dr T. R. D. Shaw, Department of Cardiology, Western General Hospital, Crewe Road, Edinburgh.

British Heart Journal, 1978, **40**, 1059-1060

Vasodilator treatment for acute and chronic heart failure[1]

Sir,

In their recent Journal article, Chatterjee and Parmley (1977) emphasise the need for measurement of left ventricular filling pressure before therapy, since impedance reduction with baseline filling pressures below 15 mmHg may result in a fall in stroke volume (Chatterjee and Parmley, 1977, *British Heart Journal*, **39**, 706). Traditionally, attainment of 'optimal' filling pressures (LVFP)—pulmonary wedge of 12 to 18 mmHg in acute myocardial infarction and pressures slightly on the 'drier' side in the adult respiratory distress syndrome —have been felt to maximise cardiac performance in the first case (Forrester *et al.*, 1971) and to prevent complicating fluid overload in the other (Moser, 1977). We would like to point out that filling pressures are but one of several factors affecting fluid exchange in the lung (Starling, 1896). Others are plasma colloid osmotic pressure, normally 20 to 25 mmHg; interstitial hydrostatic and colloid pressure, neither precisely known; and a coefficient of filtration. Despite the fact that plasma colloid osmotic pressure is now readily measurable, its influence upon cardiopulmonary function remains ignored. We believe that assessment of plasma colloid osmotic pressure may provide useful information in the management of patients for whom filling pressure assessments are crucial.

For example, in cirrhotic, crystalloid-infused, or renal failure patients plasma colloid osmotic pressure may be significantly reduced (Tremper, 1977), setting the stage for pulmonary oedema at wedge pressures formerly considered to be 'safe'. Lowering of plasma colloid osmotic pressure experimentally in animals produces pulmonary oedema (Guyton and Lindsey, 1959). In a series of 26 patients with acute myocardial infarction, it was not so much rises in left ventricular filling pressure (LVFP) that heralded pulmonary oedema as a simultaneous fall in plasma colloid osmotic pressure (PCOP), resulting in a narrowing of the PCOP-LVFP difference (Da Luz *et al.*, 1975). A recent article has suggested that large infusions of crystalloid substances (which lower plasma colloid osmotic pressure) in patients with acute myocardial infarction during therapeutic volume expansion can cause pulmonary oedema characterised by normal left ventricular filling pressure and low plasma colloid osmotic pressure (Stein *et al.*, 1975). In severe asthma, patients have been found to have very negative intrapleural pressures throughout most of the respiratory cycle (Stalcup and Mellius, 1977). Vigorous fluid therapy in these patients might decrease plasma colloid osmotic pressure, enhancing transudation of fluid into interstitium and alveolus. The effect of vasodilator therapy on plasma colloid osmotic pressure has not been specifically studied.

In summary, we believe that the desirability of vasodilator therapy in certain clinical situations, such as refractory congestive heart failure, aortic and mitral regurgitation, and myocardial infarction complicated by pump failure or shock, should not be predicated upon the presence of any 'absolute' baseline filling pressure, as Chatterjee and Parmley suggest. Rather, filling pressures should be interpreted in the context of simultaneous plasma colloid osmotic pressure measurements, and research should be directed to answering the following questions:

(1) Does plasma colloid osmotic pressure (PCOP) or PCOP-LVFP difference correlate with clinical indices of pulmonary oedema, and how does it change with pharmacological and fluid manipulations?

(2) Does PCOP or PCOP-LVFP difference correlate with morbidity and mortality in pulmonary oedema? With sudden death? With incidence of serious arrhythmias?

(3) What is PCOP in patients with respiratory failure, how does it change with therapy, and does it affect prognosis?

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[1] The opinions or assertions contained herein are those of the authors and are not to be construed as official or necessarily reflecting the views of the Medical Department of the Navy or the Naval Service at large.

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This letter was shown to Professor Chatterjee and Dr Parmley who reply as follows.

Sir,

We are in complete agreement with Drs Warren and Dennish, in that pulmonary venous pressure is one of the many factors which induce pulmonary oedema. Plasma colloid osmotic pressure is also an important determinant of interstitial oedema. In general, however, in most patients with pulmonary oedema resulting from cardiac causes, pulmonary venous pressure is the dominant factor. Furthermore, if the objective of therapy is to improve cardiac output, as well as to reduce pulmonary venous pressure, then it becomes important to determine pulmonary venous pressure before initiation of vasodilator therapy. If the pulmonary venous pressure is normal, or low, or if during vasodilator therapy there is much reduction of pulmonary venous pressure to a very low level, the stroke volume tends to decrease. We agree with Drs Warren and Dennish that absolute baseline filling pressure to differentiate between true pump failure and relative hypovolaemia is not always precise and may vary from patient to patient, but the clinical experience suggests that the filling pressure below which stroke volume tends to decrease is about 15 mmHg. These values are only suggested to provide a general guideline.

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Proceedings of the British Cardiac Society

THE 57th ANNUAL GENERAL MEETING of the British Cardiac Society was held at the Welsh National School of Medicine, Heath Park, Cardiff, on Wednesday and Thursday, 12 and 13 April 1978. The President, W. SOMERVILLE, took the Chair during private business. At the scientific sessions the Chair was taken by J. P. D. MOUNSEY.

Abstracts of Papers

Ultrasound diagnosis of superior vena caval pathway obstruction after Mustard's operation

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Superior vena caval pathway obstruction is an important cause of late morbidity and mortality after Mustard's operation. Clinical detection of such obstruction is frequently difficult because of the development of extensive collateral venous circulation, which decompresses the superior vena cava.

As flow is less likely to be normal than pressure, we recorded jugular venous flow profiles transcutaneously in 28 patients after Mustard's operation for simple transposition using a bidirectional Döppler blood velocimeter.

Twenty-four patients (86%) showed a dominant forward flow peak during ventricular diastole. Most had a normal exercise capacity and none showed any other evidence of superior vena caval pathway obstruction. This pattern was considered normal, particularly as it was also seen in 2 patients immediately after surgical relief of the anomaly. Of these 2 patients, before reoperation 1 showed an absence of pulsatile flow and the other had a forward peak during ventricular systole but reversed flow throughout diastole.

A similar forward peak during ventricular systole with, during diastole, forward flow but no peak, was seen in 2 other patients; since flow should peak when the mitral valve is open this pattern probably signifies early superior vena caval pathway obstruction.

Thus transcutaneous velocimetry is a promising technique for early detection of superior vena caval pathway obstruction, and might render further invasive investigation unnecessary.

Two-dimensional echocardiography in atrioventricular canal malformations

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Two-dimensional echocardiography (mechanical 60° sector scanner) has been applied to 9 infants and children with the angiocardiographic diagnosis of atrioventricular canal malformations. An oblique view of the normal heart can show simultaneously all 4 chambers, the junction between atrial and ventricular septa, and the anterior atrioventricular valve leaflets. In 7 patients the confluent atrioventricular septal defect was shown as discontinuity and asynchronous movement between the contiguous parts of the atrial and ventricular septa; in 2 patients the atrial septum was not seen (single atrium at surgery and large ostium primum defect at necropsy). A single wide echo represented a common anterior atrioventricular valve leaflet (CL), apparently attached to the ventricular septum in 7. Left ventricular injection of 'ultrasonic contrast' in 3 patients suggested shunting directly to the right ventricle in 1 (CL not attached to ventricular septum on echocardiography) and to the atria in 2 (CL attached to ventricular septum). These preliminary studies suggest that the 4-chamber view combined with contrast echocardiography should make possible the differentiation of partial atrioventricular canal and type A complete atrioventricular canal from complete atrioventricular canal types B and C.

Papillary muscle echoes in hypertrophic obstructive cardiomyopathy

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From a previous echocardiographic study (Rodger, 1976) of hypertrophic obstructive cardiomyopathy (HOCM), we concluded that the echoes intervening in systole between the interventricular septum and the mitral anterior leaflet originate from the posterior papillary muscle and its chordae tendineae.

The hypothesis has been re-examined: 7 patients with HOCM have been investigated by single and multiple beam echocardiography. On the single beam scans, systolic anterior motion of the mitral apparatus preceded anterior motion of the left ventricular posterior wall and the apparent continuity between posterior wall echoes and the muscular component of the mitral echo complex was found to be spurious. Multiple beam scanning in the transverse and oblique axes of the left ventricle showed that the structure intervening between the septum and the mitral anterior leaflet in systole was in continuity with the anterolateral wall of the left ventricle and moved anteromedially during systole. This structure was not recorded on longitudinal scans during diastole.

It is concluded that in HOCM the echoes recorded in systole between the septum and the mitral anterior leaflet originate from the anterior papillary muscle and its chordae, and that displacement of these structures is responsible for systolic anterior motion of the mitral leaflets.

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Major arrhythmias in aortic stenosis detected by 24-hour ambulatory monitoring

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The true incidence of serious cardiac arrhythmias in patients with haemodynamically significant aortic stenosis has not been previously defined. In the present study 24-hour ambulatory electrocardiographic tape recordings were made in 40 patients requiring aortic valve replacement. At least two recordings were made before operation and repeated in the early (1 to 7 days) and late (2 to 3 months) postoperative periods.

Episodes of advanced atrioventricular block or asystole were detected in 6 of 40 patients (15%) and managed routinely by pacemaker implantation. Ventricular arrhythmias were detected in 87·5 per cent of patients before operation. Importantly, 7 of 40 patients (17·5%) developed malignant ventricular arrhythmias, for example ventricular tachycardia and ventricular fibrillation. Prodromal ventricular arrhythmias, including premature beats >60 per hour, and those occurring from multiple foci, in couplets or of R-on-T type, occurred in 85 per cent of patients before operation. Angiographically shown obstructive coronary artery disease or impaired left ventricular function predisposed to malignant ventricular arrhythmias before operation, but there was no clear correlation with aortic valve gradient. The high incidence of malignant ventricular arrhythmias in the preoperative and late postoperative periods suggests that antiarrhythmic therapy should be evaluated in all patients with severe aortic stenosis on diagnosis, during and after recovery from aortic valve surgery.

Spontaneous termination of paroxysmal re-entrant supraventricular tachycardia; mechanisms and implications for rational prophylactic or emergency therapy

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By continuously recording the blood pressure and performing tilt tests during intracardiac electrophysiological studies in 16 patients with paroxysmal re-entry atrioventricular tachycardia we have shown a relation between the 4 phases of reflex autonomic activity restoring the blood pressure and the mechanisms of termination of paroxysmal re-entry atrioventricular tachycardia. These phases are: (1) profound hypotension with normal autonomic tone; (2) blood pressure rise because of increased sympathetic and decreased vagal activity; (3) blood pressure 'overshoot' response; and (4) established tachycardia with new stable blood pressure and autonomic reflex activity.

Paroxysmal re-entry atrioventricular tachycardia often terminates spontaneously by a mechanism of self-induced second degree block in one of the two atrioventricular pathways when the frequency of reciprocation exceeds the Wenckebach rate for this component of the circuit; the less the discrepancy between these two rates, the likelier it is that spontaneous termination will occur by this mechanism. When the site of spontaneous termination is the atrioventricular node, the attack may stop in either phase 1 or phase 3 when vagal tone is normal. Head-down tilt or atrioventricular nodal depressant drugs favour this mechanism and allow those in phase 4 to regain the more favourable phase 3 situation and thereby an enhanced likelihood of termination. Quinidine-like drugs may be either ineffective or indeed detrimental.

Conversely, spontaneous termination occurs most readily in the extra-atrioventricular nodal pathway in phases 2 and 4 and with head-up tilt. Quinidine-like drugs favour this mechanism while atrioventricular nodal drugs may be detrimental. When prophylaxis against re-entry fails, an alternative approach is to encourage early spontaneous termination of paroxysmal re-entrant atrioventricular tachycardia in either the atrioventricular node or extra atrioventricular nodal pathway, with appropriate antiarrhythmic drugs and postural change.

Effect of exercise, isoprenaline, and propranolol on left ventricular function in normal subjects and patients with angina as assessed by nuclear angiography

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To make a detailed assessment of the value of nuclear angiography in measuring changes in ventricular function, we studied the effects of exercise followed by beta-stimulation and beta-blockade in 8 normal subjects and 4 patients with angina pectoris. We measured ejection fraction by the bolus technique (Hannan *et al.*, 1977) and generated ventricular volume curves by the re-triggered method (Muir *et al.*, 1977).

During dynamic supine leg exercise normal subjects increased their ejection fraction from 0·58 to 0·71, but patients with angina showed no change or even a decrease in ejection fraction.

After infusions of isoprenaline at 0·75, 1·0, and 2·0 μg/min the ejection fraction increased in all subjects from a resting value of 0·58 to 0·72, 0·74, and 0·76, respectively. Both the mean ejection rate and the peak rate of change of volume during systole (dVs/dt) increased while the mean ejection time decreased progressively with increasing doses of isoprenaline. The changes in peak rate of change of volume in diastole (dVd/dt) and the mean diastolic filling time (td) were variable and probably of little significance.

After propranolol (0·2 mg/kg body weight) all the variables returned to control values and were unchanged by subsequent reinfusion of isoprenaline at a rate of 2·0 μg/min.

Our results show nuclear angiography to be valuable in assessing changes in ventricular function. Of particular interest is the divergent effect of isoprenaline and exercise on ejection fraction in patients with angina; this warrants further investigation.

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Localisation of coronary artery disease by thallium-201 stress myocardial scintigraphy

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Myocardial imaging using thallium-201 (^{201}Tl) administered during maximal exercise has been performed in 4 projections in over 100 patients with ischaemic heart disease to determine the pattern of scintigraphic uptake defects associated with specific coronary lesions seen on angiography.

A triad of defects was found in left anterior descending disease, viz. an apical wedge defect in 70 per cent of lesions, a septal uptake defect in 85 per cent of lesions, and a defect seen only in the left lateral projection in 72 per cent of lesions.

We have called this last defect a diagonal window because it was found with independent disease of the diagonal branch of the left anterior descending or with main trunk left anterior descending disease occurring before this branch. It was the most useful scintigraphic sign for differentiating proximal from distal disease in the left anterior descending and had a specificity of 90 per cent.

False negative scintigraphic defects occurred more frequently in triple vessel disease and in association with well-developed coronary collaterals.

Severe left anterior descending disease occurring without an apical wedge defect was associated with an excellent calibre of the distal left anterior descending lumen in 25 out of 28 patients (89%).

Specific scintigraphic patterns of ^{201}Tl myocardial uptake appear valuable in the non-invasive localisation of left anterior descending disease and in the planning of aortocoronary bypass graft operations.

Exercise radionuclide ventriculography: assessment of changes in global left ventricular function, and in function of contractile segments in patients with left ventricular aneurysms

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Thirteen patients with left ventricular aneurysms had first pass radionuclide ventriculograms performed at rest, and at submaximal supine exercise before and after afterload reduction with 5 mg sublingual isosorbide dinitrate. Ejection fraction of the left ventricular contractile segment was calculated from the resting isotope study and the contrast cineangiogram, using the double hemispheroid model, and a modified area-length method. From the 2 techniques, it correlated closely ($r = 0{\cdot}86$).

At exercise total left ventricular ejection fraction, measured from the high frequency fluctuation in radioactive counts over the left ventricle, increased in 6 patients, decreased in 5, and was unchanged in 2. Ejection fraction of left ventricular contractile segment increased in 7, including 5 in whom left ventricular ejection fraction increased, and ejection fraction of left ventricular contractile segment fell in 5, of whom 4 had decreased left ventricular ejection fraction.

After afterload reduction, at the same level of exercise, left ventricular ejection fraction increased for the whole group ($P < 0{\cdot}01$) and mean pulmonary transit times fell significantly ($P < 0{\cdot}01$).

Of 7 with increased ejection fraction of contractile segment, 5 improved further after isosorbide dinitrate ($P < 0{\cdot}05$), and 2 with initially decreased ejection fraction of contractile segment improved exercise levels conspicuously after isosorbide dinitrate.

Exercise first pass radionuclide ventriculography can accurately estimate the ejection fraction of the contractile segment, an important factor in predicting the prognosis of aneurysmectomy. Changes in the contractile segment on exercise and with afterload reduction may be a further guide in the selection of patients for aneurysmectomy.

Relation between coronary anatomy, myocardial perfusion, and praecordial electrocardiographic signs in coronary artery disease

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Exercise electrocardiography is used to identify myocardial ischaemia in patients with anginal chest pain. However, it is necessary to investigate the relation between disturbances of regional perfusion and electrocardiographic signs of myocardial ischaemia.

Twenty-eight patients with anginal pain underwent 16 point praecordial electrocardiographic mapping before and after exercise. The area, severity, and time course of ST segment depression and Q waves were measured in serial praecordial maps. These patients underwent coronary and left ventricular angiography. A catheter was positioned in the aortic sinuses and $^{81}\mathrm{Kr}^{m}$ was continuously infused at rest and during cardiac pacing. Regional myocardial activity was recorded to examine moment to moment changes in regional myocardial perfusion.

The results fell into four groups. The first group with normal coronary arteries had uniform ventricular perfusion and normal praecordial electrocardiographic maps during stress. A second group with coronary artery disease (lesions $> 70\%$) showed fixed defects of perfusion and corresponding praecordial areas of Q waves. A third group with coronary artery disease (lesions $> 70\%$) had reversible disturbances of regional perfusion associated with praecordial areas of ST segment depression during stress. The last group with coronary artery disease (lesions $> 70\%$) had uniform ventricular perfusion and normal praecordial electrocardiogram during stress.

This study suggests that there is a relation between disturbances of regional myocardial perfusion and the praecordial electrocardiographic signs of myocardial ischaemia in these patients.

What does *not* cause ischaemic heart disease?

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Cardiology, Welsh National School of Medicine,
Cardiff

High mortality from ischaemic heart disease in England and Wales is associated with (1) low temperature, (2) high rainfall, (3) low drinking water calcium, and (4) low socioeconomic class. Epidemiological studies relating disease mortality to socioenvironmental factors can help elucidate aetiology but need to be interpreted with caution. *First,* the relation must be shown to be causal. For example, our analyses of 1969 to 1971 mortality data in England and Wales indicate that water hardness is a confounding and not a causal variable: pairs of communities using hard and soft water but similar in other respects show similar mortality from ischaemic heart disease. *Second,* the relation must be shown to be disease specific and not the result of non-specific association with earlier death from all causes. We have shown that the four socioenvironmental variables listed above are associated with general mortality and not specifically with mortality from ischaemic heart disease; it appears therefore that they act through influencing the age of death irrespective of its cause. Geographical variations in mortality from ischaemic heart disease are not associated with similar variations in age-standardised proportional mortality from ischaemic heart disease.

Exercise testing and thallium-201 myocardial perfusion imaging in evaluation of aortocoronary bypass surgery

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Fifteen patients presenting with angina pectoris underwent exercise evaluation using a bicycle ergometer, and myocardial perfusion imaging using thallium-201 (^{201}Tl) before and after aortocoronary bypass surgery.

After operation 12 patients were symptom free, 2 had moderate exercise limitation by breathlessness without angina, and 1 was symptomatically unaltered with continuing angina. Using a standardised exercise procedure exercise duration averaged 8·45 (±3·23) minutes before operation and 10·32 (±2·31) minutes after operation ($P < 0{\cdot}1$). Maximal heart rate achieved during exercise rose from 134 (±24)/minute before operation to 157 (±17)/minute after operation ($P < 0{\cdot}01$).

The exercise electrocardiogram showed evidence of ischaemia in 12 patients before operation. After operation one patient had new Q waves suggesting perioperative myocardial infarction. In 8 patients the exercise electrocardiogram showed no evidence of ischaemia, while in 3 patients, though less pronounced, electrocardiographic evidence of ischaemia persisted.

Before operation 14 patients had defects on exercise ^{201}Tl images consistent with ischaemia. After operation ^{201}Tl imaging suggested complete revascularisation in 10 patients with partial revascularisation in 2 patients (one with continuing angina). Perioperative myocardial infarction was seen in 2 patients. In addition there were small areas of apparent myocardial necrosis in 3 patients.

^{201}Tl myocardial imaging is a useful technique to assess aortocoronary bypass surgery, both to provide evidence of relief of myocardial ischaemia and to show myocardial damage occurring in the perioperative period.

Craniocaudal tilt in angiocardiographic visualisation of congenital heart defects

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The interventricular septum normally spirals in a clockwise fashion as it courses posteriorly and superiorly from the apex of the heart to its base.

In order to visualise its maximum length with a fixed posteroanterior *x*-ray beam, head-up tilt of the patient is required. Different degrees of rotation about the patient's longitudinal axis will bring the atrial, and inflow, trabecular, perimembranous, and infundibular components of the ventricular septum in line with this beam. Injections of contrast medium on the appropriate side of the septum to be investigated will profile and display defects in it.

Atrioventricular canal defects are characterised by a constantly abnormal relation of the mitral component to the interventricular septum. Interatrial and interventricular components of the defect can be distinguished easily, because the right atrium and right ventricle do not overlap.

As this view also displays the left ventricular outflow tract throughout its length, obstructions there are better defined than in conventional projections which cause foreshortening. The anatomy of the aortic arch and pulmonary artery bifurcation (given appropriate obliquity) is also well shown.

Having performed over 200 such angiocardiograms, we are persuaded that oblique projections with craniocaudal tilt are the best method, particularly for left ventricular angiocardiography.

Demonstration of aortopulmonary communications using a balloon angio-catheter

H. C. Mulholland
Royal Victoria Hospital, Belfast

Major aortopulmonary communications are often present in cyanotic congenital heart disease. Demonstration of the size and distribution of these vessels is of importance before operation. This is commonly done by retrograde aortic catheterisation and selective arteriography of individual collateral vessels. However, this method is tedious, requires multiple injections, and may not show all major communications. A technique is described which provides good definition of major collateral vessels using only one injection of contrast.

A balloon angio-catheter is floated anterogradely along the aorta until the tip is distal to the area of interest. Immediately before contrast is injected the balloon is fully inflated, producing near total obstruction to forward flow in the descending aorta. Contrast is then injected into the aorta just proximal to the balloon. Obligatory flow occurs through vessels arising from that portion of the aorta and anastomoses are clearly defined. The technique has been used in 12 children aged 2 days to 7 years (weight 2·5 to 20 kg). After obstruction to forward flow the systolic blood pressure increased by a mean of 20 mmHg. Injection of contrast caused a further small transient rise. No adverse effect occurred in any patient after balloon inflation or contrast injection. The technique has wide application in cyanotic congenital heart disease.

Working capacity of children with transposition of the great arteries after Mustard repair

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A Mustard repair provides physiological correction. Of the late survivors, 75 per cent are leading normal lives with little or no exercise intolerance. The working capacity of 22 patients with transposition of the great arteries was studied 5 to 10 years after operation.

Ten patients were corrected in infancy (mean age 9 months), and in this group the mean age at time of study was 7·3 years (6·75 to 9·3 years). A further 12 patients were corrected later (mean age 3·3 years) and studied at a mean age of 11·7 years (9 to 18 years). A progressive exercise test was performed, recording heart rate and ventilation, and measuring gas exchange.

Of the patients corrected in infancy, 9/10 achieved a normal maximum work load, as did 4/12 of the older group, the remainder being just below normal ($P < 0{\cdot}025$). The maximum oxygen consumption measured showed the same trend. The ventilation was abnormally high in relation to carbon dioxide production in the infant operated group, but also tended to be high in the older group. Of all patients, 59 per cent were in sinus rhythm at time of study, but neither maximum work load nor maximum oxygen consumption was influenced by the type of rhythm present.

Thus, the working capacity of children undergoing Mustard repair in infancy is within normal limits, but is just below the normal range in those corrected later. A longitudinal study will show whether the infants maintain a normal capacity with growth.

Primary total correction of tetralogy of Fallot under age of 2 years: results of 50 consecutive unselected cases

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M. Yacoub
Harefield Hospital, Middlesex

Between 1972 and 1977, 50 consecutive patients under the age of 2 years with tetralogy of Fallot requiring operation underwent primary total correction irrespective of their age or the anatomy of the lesion. The ages of the patients were between 2 and 24 months. Twenty (40%) were operated upon as emergencies, because of cyanotic attacks. Four patients had hypoplastic pulmonary arteries. Twenty-one (42%) required reconstruction of the right ventricular outflow tract with homografts. There were 9 early deaths: 5 of these patients were receiving propranolol before the operation. There have been no late deaths. The 41 survivors have been followed up for between 12 and 72 months. One patient has required reoperation for an aneurysm of the right ventricular outflow tract and is now well. The remaining patients are asymptomatic and developing normally. Thirty-one have been reinvestigated routinely 1 to 60 months after operation. Twenty-nine patients had a RV/LV ratio of below 0·35. There was no evidence of residual ventricular septal defect in any patient.

It is concluded that primary total correction of tetralogy of Fallot can give satisfactory results even if there is unfavourable anatomy provided that the patients have not received propranolol; and that adequate relief of the outflow tract obstruction, with or without homograft reconstruction, gives maintained good results.

Applied anatomy of coronary arteries in univentricular hearts

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(introduced by G. A. H. Miller)
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The diagnosis and surgical correction of univentricular hearts remains a challenge. The coronary artery anatomy, its relation to morphological characteristics, and its surgical implications have been analysed in 26 necropsied specimens of univentricular heart, all but 2 having undergone operation (18 septation, 6 palliation).

Twenty-one had a morphologically left ventricular main chamber with an anterior outlet chamber, 17 left-sided subaortic, 3 right-sided subaortic, and 1 right-sided subpulmonary. Delimiting arteries outlined the outlet chamber in 16 of these hearts. Major anterior delimiting parallel branches of the right coronary coursed over the front of the heart in all but 1, and 13 had been interrupted with resultant ischaemic myocardial injury.

Five hearts were without outlet chamber, 2 with morphologically left ventricular and 3 with morphologically right ventricular main chamber. Rudimentary pouches were present in 3, in 1 anteriorly and in 2 posteriorly. The 2 lying posteriorly were not outlined by delimiting arteries. Two of this group had coronary artery injury.

Identification of outlet chambers and rudimentary pouches is facilitated by knowledge of coronary anatomy. The presence of major right anterior delimiting parallel arteries over the usually favoured ventriculotomy site renders them vulnerable to surgical injury, exemplified by such mishap occurring in 15 of 18 septated hearts.

Preservation of renal tubular function during cardiopulmonary bypass using pulsatile flow

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Pulsatile blood flow has many physiological advantages over non-pulsatile flow. It is now possible to deliver pulsatile flow with standard cardiac bypass using a pulsatile device and balloon pump module.

We looked at the effect of pulsatile flow on renal function in 20 patients undergoing elective coronary artery surgery, half receiving pulsatile flow on a random basis. The free water clearance, a sensitive indicator of renal tubular function, was measured before, during, and after bypass. Urine flows and diuretic usage were noted.

A previous study showed that free water clearance (normal range -25 to -100 ml/hr) deteriorates during bypass, reverting to normal 24 hours after operation. We confirmed these findings, but in patients receiving pulsatile flow free water clearance remained within the normal range. Urine flow during bypass in the non-pulsatile group was a mean of 87 ± 60 ml/kg per hr compared with 165 ± 120 ml/kg per hr in the pulsatile group ($P = 0{\cdot}05$). Furthermore, half the patients in the non-pulsatile group required diuretics during and after bypass compared with one patient in the pulsatile group. No patients studied developed renal insufficiency in terms of increased urea or creatinine.

We conclude that pulsatile flow maintains normal renal tubular function during cardiac bypass, and may be useful in patients with preoperative renal insufficiency or those undergoing long bypass procedures.

Bromocriptine in methyldopa treated hypertension: possible role of central dopaminergic activity

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Methyldopa increases serum prolactin, probably by reducing effective central dopaminergic activity. Bromocriptine is a dopaminergic agonist. We have studied the effects of bromocriptine therapy in 10 hypertensive patients already taking only methyldopa (0·5 to 3·0 g/day). After baseline measurements, optimal dosage of bromocriptine was achieved (7·5 to 20 mg/day), and bromocriptine was then replaced by placebo on a double-blind basis. Supine and erect, systolic and diastolic blood pressures were significantly reduced by bromocriptine. Serum prolactin fell significantly. Total exchangeable body sodium, 24-hour urinary sodium and potassium excretion, and serum angiotensin levels were not significantly altered. Three patients lost pre-existent ankle swelling but there was no mean weight loss. All patients volunteered that they experienced an improvement in well-being, with loss of impotence in one. The antihypertensive effect of bromocriptine may be the result of increased central dopaminergic activity and/or of a reduction in prolactin-mediated salt and water retention.

Effects of oxygen administration, bicarbonate infusions, and brief hyperventilation on patients with pulmonary vascular obstructive disease

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Killingbeck Hospital, Leeds

In an attempt to clarify further the mechanisms underlying labile rises in pulmonary vascular resistance, the effects of administering high oxygen concentrations, brief voluntary hyperventilation, and correction of acidosis were studied in 16 patients in whom congenital heart disease was associated with pulmonary vascular disease. On breathing 100 per cent oxygen there was a significant fall in pulmonary vascular resistance from 21·8 ± 4·6 to 12·9 ± 3·6 units m^2 ($P < 0{\cdot}001$), with a rise in pulmonary blood flow from 4·4 ± 0·6 to 8·8 ± 2·0 litres/min per m^2 ($P < 0{\cdot}025$) and a fall in pulmonary artery pressure from 67·8 ± 2·8 to 61·8 ± 4·0 mmHg ($P < 0{\cdot}025$). The changes occurring on sodium bicarbonate administration in 6 patients did not reach levels of significance, but the size of each individual response was closely correlated with the response to oxygen administration. No significant changes occurred either on voluntary hyperventilation or in the systemic circulation with any intervention. However, systemic vascular resistance was positively correlated with pulmonary vascular resistance ($P < 0{\cdot}01$). As a result of this, though age was correlated positively with both pulmonary artery mean pressure ($P < 0{\cdot}025$) and vascular resistance ($P < 0{\cdot}025$), it was not correlated with the ratio of pulmonary to systemic resistance. Since pulmonary vascular disease is progressive, these results cast some doubt on the validity of resistance ratio as a measure of its severity.

Effect of triac and propranolol on developing myocardium in rats

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National Heart Hospital, London; Royal Free Hospital, London; and Nuffield Institute of Comparative Medicine, London

In long-standing cases of hyperthyroidism, cardiomyopathy may result and analogues of thyroid hormones, for example triac (triiodothyroacetic acid), could play a part in causing heart muscle disease.

To study experimentally the effect triac may have on the developing myocardium, 60 μg triac per day alone, and in combination with 50 μg propranolol per day, were administered intramuscularly to pregnant rats for 15 days. Another group was given 50 μg propranolol per day only, and a final group, receiving buffer solution alone, served as controls. No further injections were given to the newborn rats, which were killed at intervals varying between 2 and 56 days after birth. Samples of myocardium were examined histologically, histochemically, and ultrastructurally.

In the group of young rats where the parent had received triac alone, severe changes of hypertrophy with extensive disarray of myofibrils were observed ultrastructurally, similar to those of hypertrophic cardiomyopathy in man. Disarray was not observed histologically. At day 56, this irregular arrangement was lost and hypertrophied myocardium was found. In the triac and propranolol group, hypertrophy was consistently observed without significant disarray at any stage during the experiments. Propranolol alone showed no effect on the myocardium.

It is concluded that triac produces profound changes in the myocardium of developing rats, simulating hypertrophic cardiomyopathy, and that propranolol appears to protect the myocardium from this disarray. The implication of these findings to the human situation are discussed.

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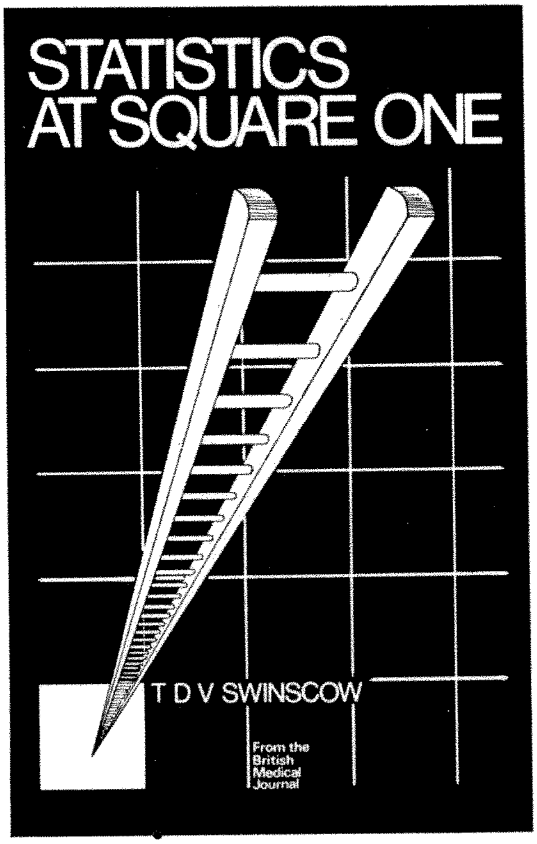

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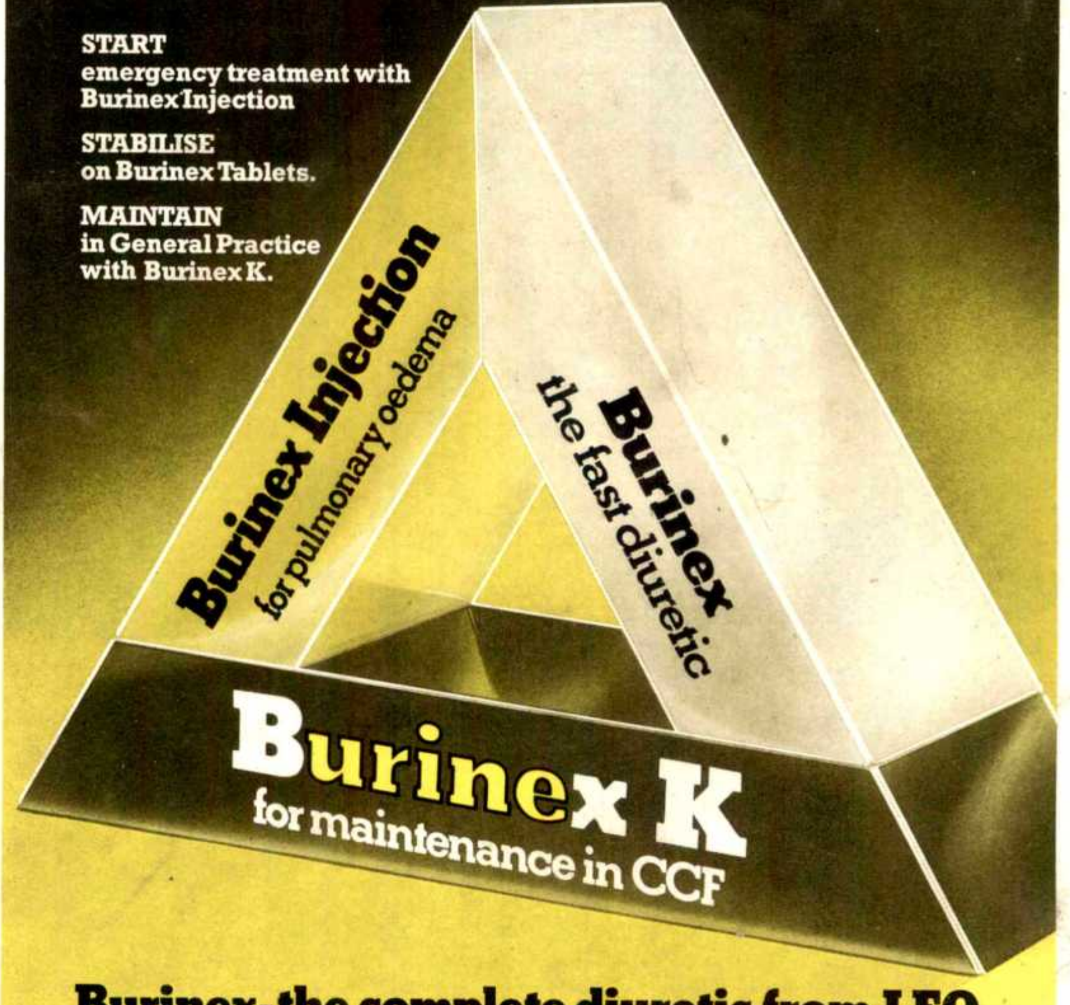

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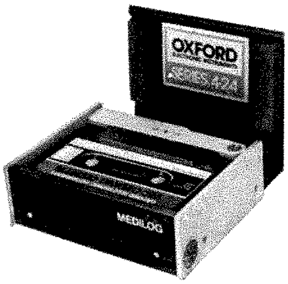

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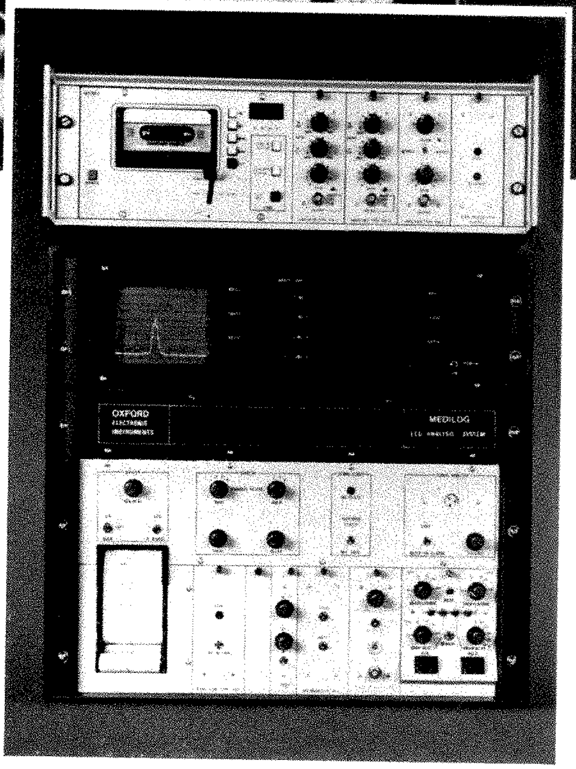

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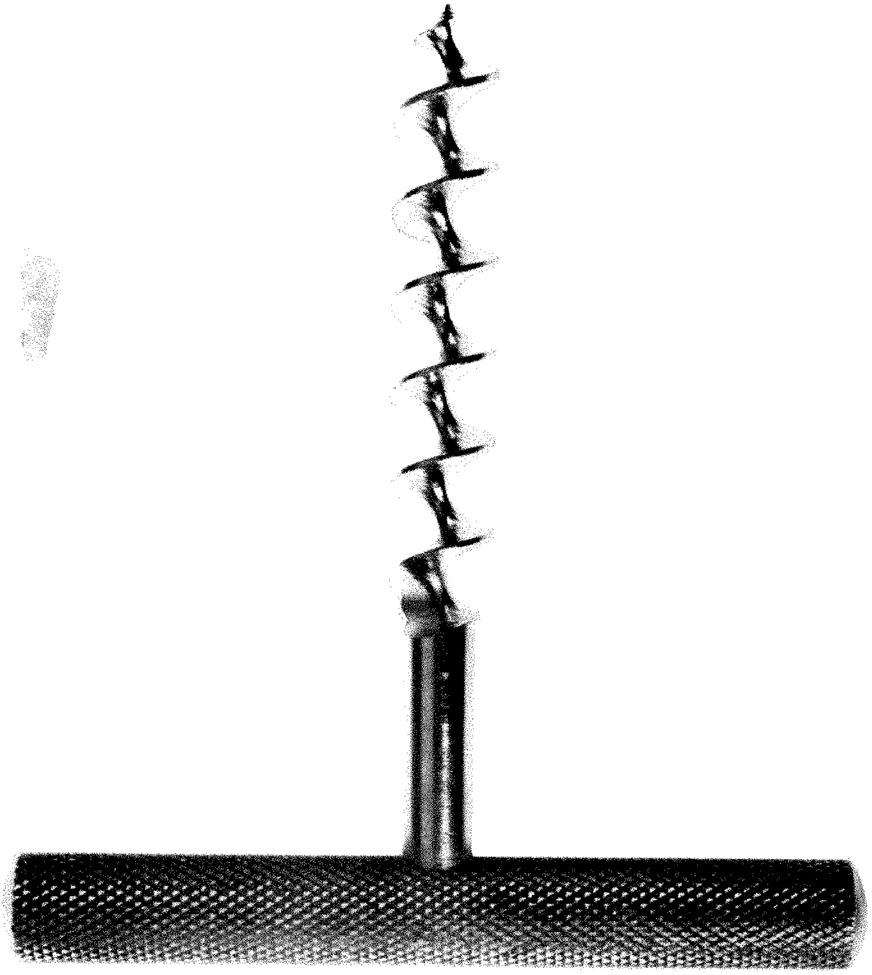

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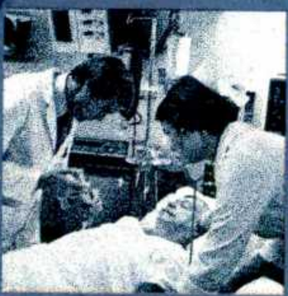

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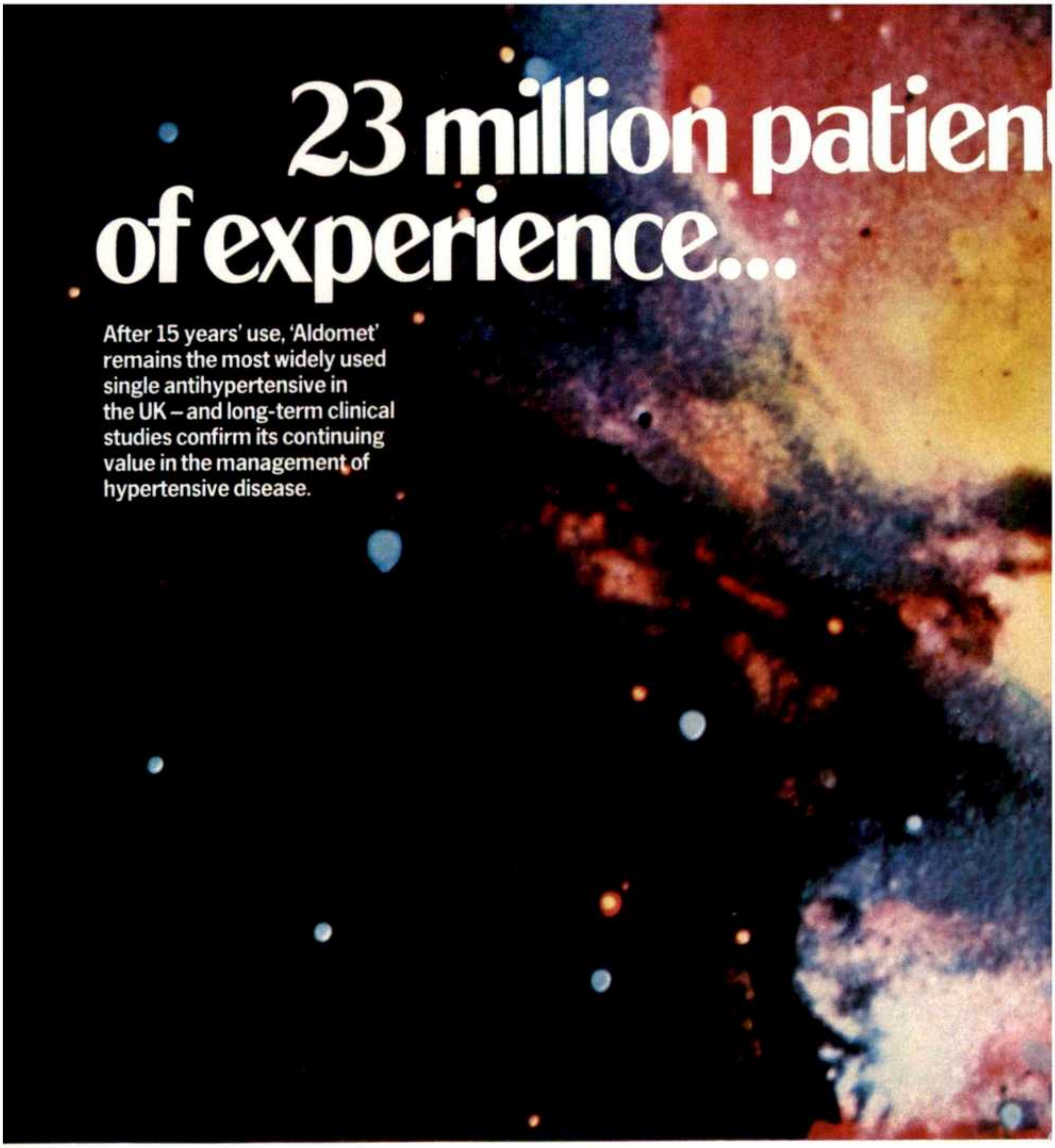

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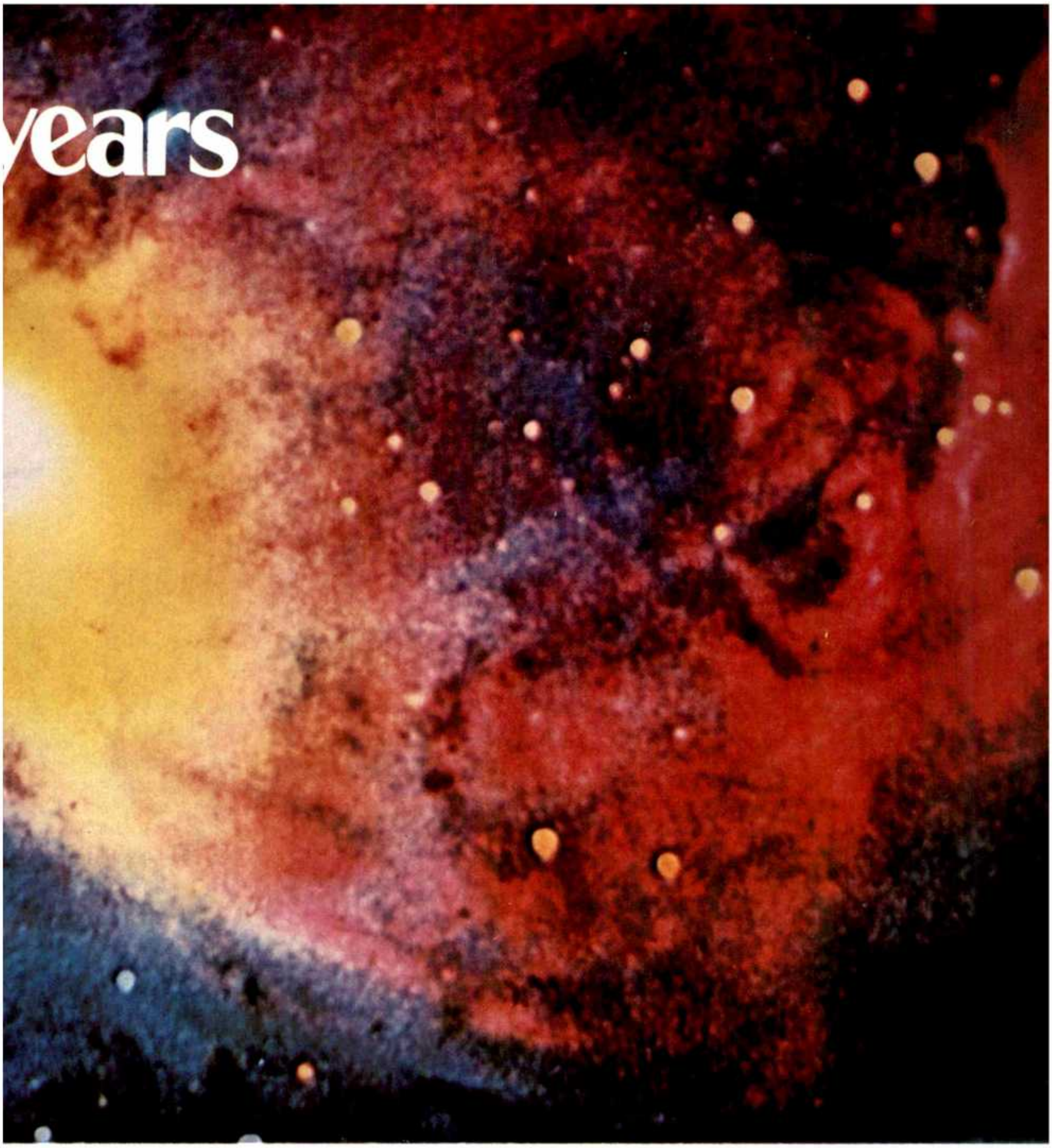

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Speakers

Cardiovascular Surgery: William L. Ashburn, M.D., Charles Dubost, M.D., Paul A. Ebert, M.D., W. Dudley Johnson, M.D., Bok Y. Lee, M.D., Frederick Merkel, M.D., Julian Morales Rocha, M.D., Patricia A. Randall, M.D., J. Vollmar, M.D.
Cardiovascular Diseases: Daniel S. Berman, M.D., Kanu Chatterjee, M.D., Tom Madhavan, M.D., Attilio Maseri, M.D., Henry N. Neufeld, M.D., Ronald J. O'Reilly, M.D., Bertran Pitt, M.D., Leon Resnekov, M.D.
Hypertensive Diseases: Frank A. Finnerty, Jr., M.D., Haralambos Gavras, M.D., Ray W. Gifford, Jr., M.D., Ellin Lieberman, M.D., Gurdarshan S. Thind, M.D., Yukio Yamori, M.D.

Topics

Monday, January 15 **Cardiovascular Surgery**

Surgical Considerations of Coronary Artery Diseases Associated with Other Conditions Requiring Operation ● Emergency Thoracic Aortography—Indications, Techniques, Results ● Constrictive Fibrous Endocarditis: New Surgical Treatment ● Nontraumatic Measurement of Ventricular Function Using Nuclear Imaging Renal Autotransplantation for Vascular Disease ● Advances in the Treatment of Congenital Heart Disease ● Prevention of Deep Venous Thrombosis ● Advances in Reconstructive Venous Surgery ● Re-evaluation of Bypass Surgery ● Experience with Mitral Valve Surgery.

Tuesday, January 16 **Cardiovascular Diseases**

Two-Dimensional Echocardiography in Clinical Cardiology ● Clinical Applications of Vasodilator Therapy for Heart Disease ● Coronary Angiography and Normal Left Ventricle Vascular Anatomy ● Early Rehabilitation after Myocardial Infarction ● Antibiotic Treatment of Infective Endocarditis ● Diagnosis and Treatment of Vasospastic Angina Pectoris ● Myocardial Infarct Sizing ● Radioactive Tracer Techniques to Evaluate Coronary Artery Disease ● Cardiovascular Nuclear Medicine: Clinical Applications.

Hypertensive Diseases

Management Problems in Hypertension ● Childhood Hypertension ● Hypertensive Diseases in Stroke-Prone SHR ● Office Management of the Hypertensive Patient ● The Role of the New Enzyme Inhibitors in Hypertension ● Evaluation of the Hypertensive Patient ● New Antihypertensive Agents.

Wednesday, January 17—ONCOLOGY. Chairmen: R. Lee Clark, M.D. and Joseph T. Painter, M.D.
Thursday, January 18—NUTRITION/HYPERALIMENTATION. Chairman: George L. Blackburn, M.D.
Friday, January 19—RHEUMATOLOGY. Chairmen: Andrei Calin, M.D. and James F. Fries, M.D.

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1. *Br. J. Anaesth.* (1977) **49**, 251
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4. *Arch. gen. Psychiat.*, accepted for publication

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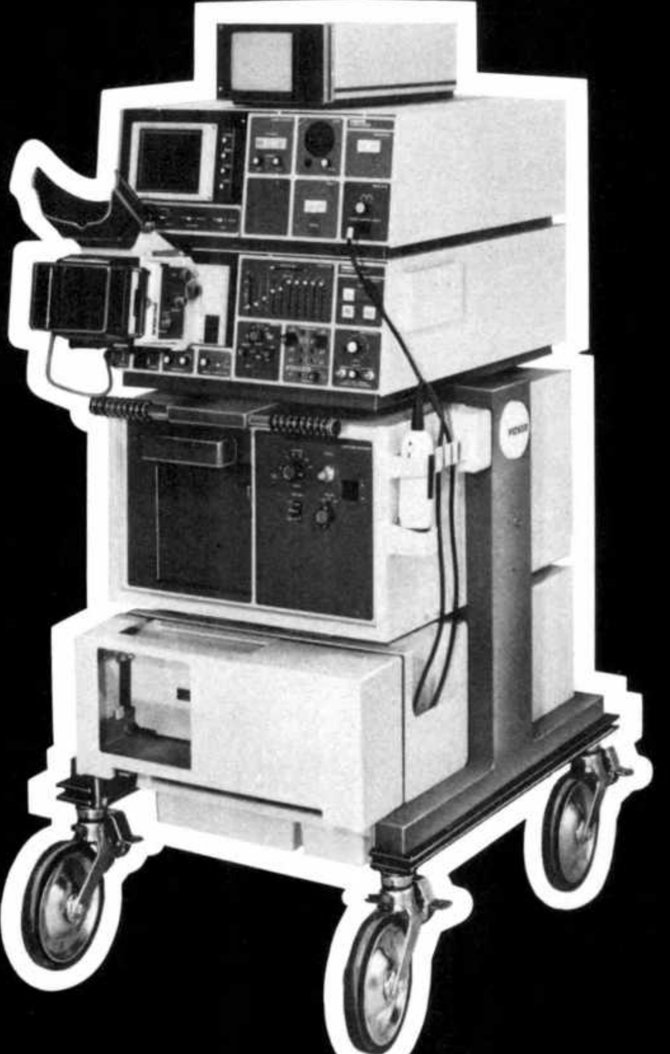

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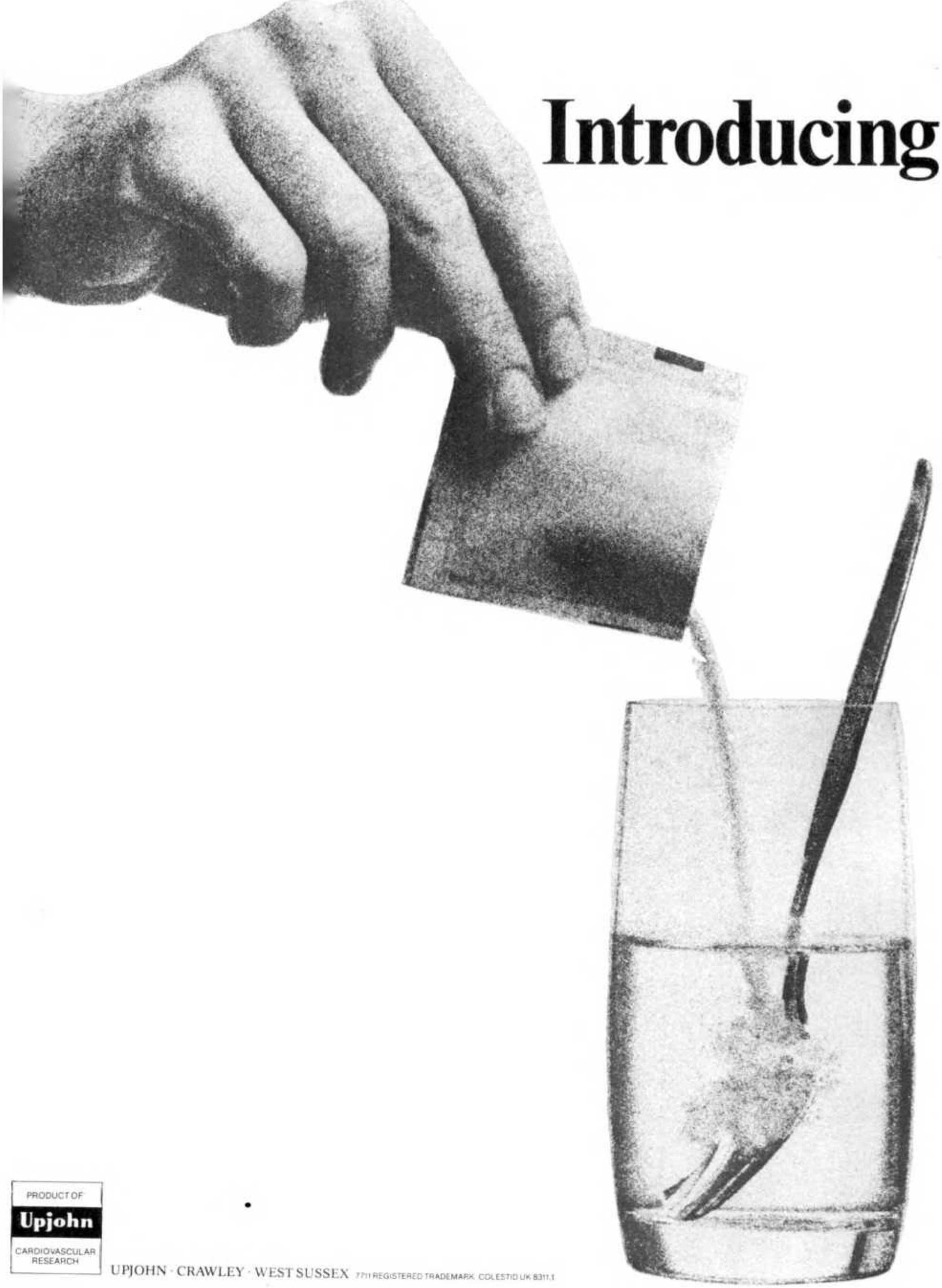

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Colestid has produced no known interference with the action of coumarin anticoagulants, making it suitable for patients already under treatment for a heart condition. However, since Colestid may interfere with the absorption of certain drugs (e.g., chlorothiazide, tetracycline and penicillin G), the clinical response to concomitant medications should be closely monitored and appropriate adjustments made.

Most patients tolerate Colestid therapy very well. The most common side effect is mild constipation.

References: 1. Med. J. Aust. (1973). *1*:1223.
2. JAMA (1972). *222*:676.
3. New Zealand J. Med. (1972). *76*:12.

Prescribing Information

Presentations: Tasteless and odourless granules of colestipol hydrochloride. *Uses:* Adjunctive therapy to diet for treatment of hypercholesterolaemia, particularly Frederickson Type II. *Dosage and Administration:* Always mix with water or other fluids before ingesting. Oral total daily dosage for adult 15–30 grams. Take in divided doses 2–4 times daily. *Contraindications:* Hypersensitivity to colestipol. *Precautions, Warnings:* Not to be taken in dry form. Colestid may interfere with absorption of some drugs (e.g. penicillin G, tetracycline, chlorothiazide). Safety for use in pregnant women or children not established. *Package Quantities:* 30 x 5 g sachets; 250 g bottle. Each sachet or scoopful contains 5 g colestipol hydrochloride. *Further Information:* Colestid is not absorbed. It binds bile acids causing further cholesterol conversion to bile acids thus lowering serum cholesterol levels. *Basic NHS Costs:* 30 x 5 g sachets £8.90. 250 g bottle £13.76. Product Licence Nos. PL 0032/0055. PL 0032/0057. *Full Product information is available on request.*

Published September 1978

Supplement to BRITISH HEART JOURNAL

PREVENTION OF ARRHYTHMIAS

The Proceedings of a Symposium held at Freeman Hospital, Newcastle upon Tyne, on 12 and 13 September 1977, arranged by Professor D. G. Julian

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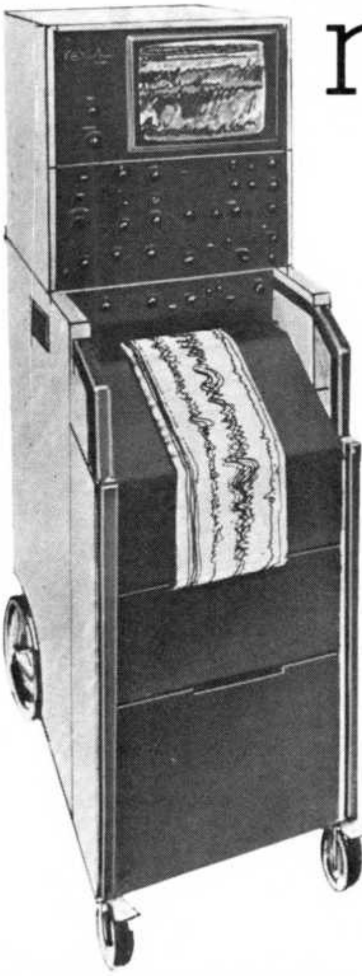

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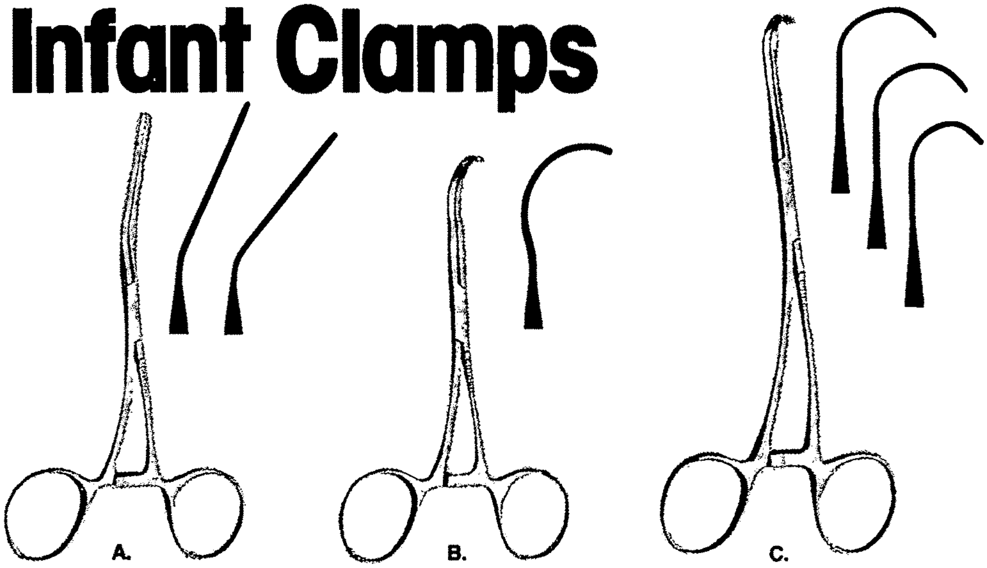

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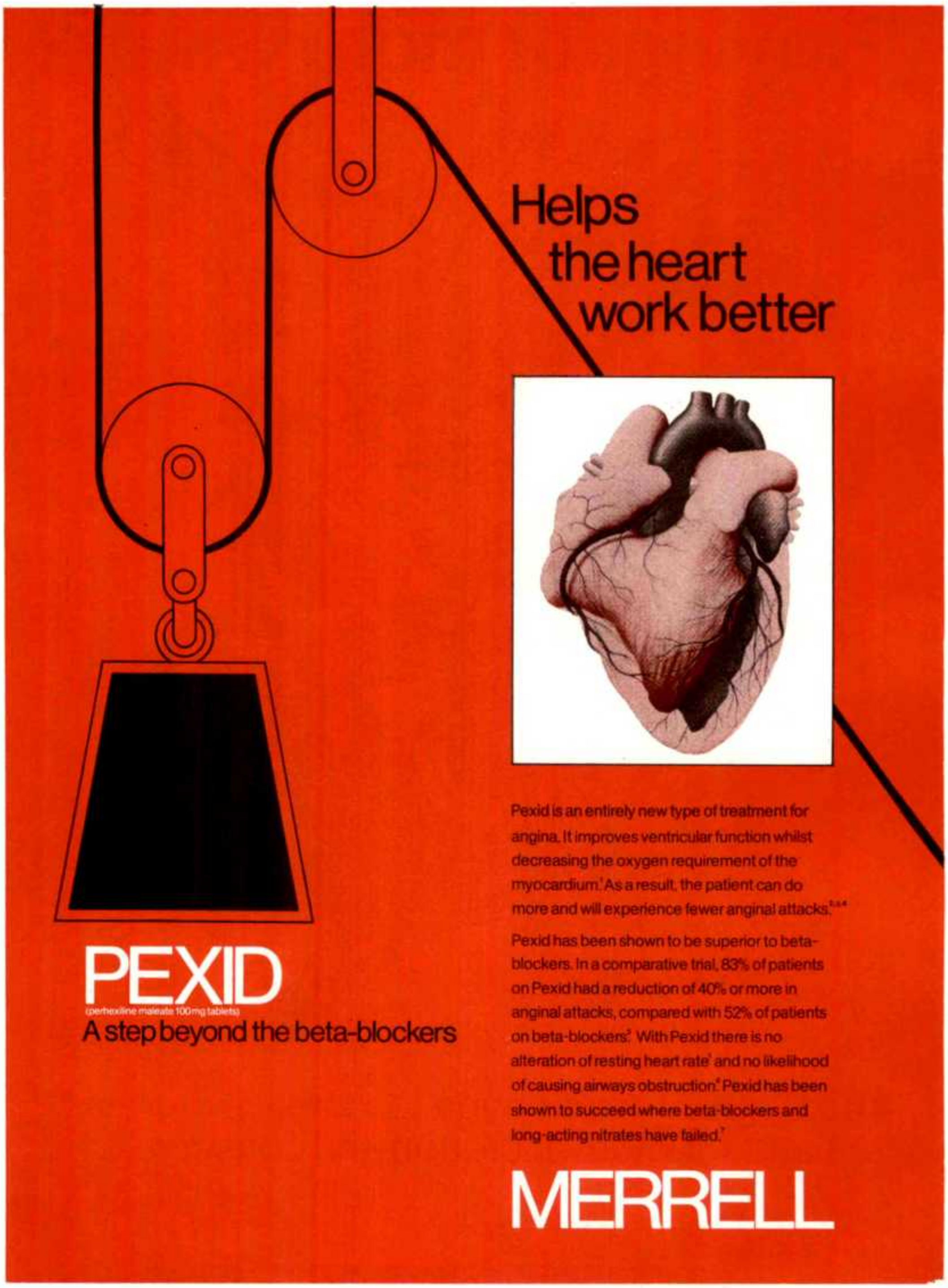
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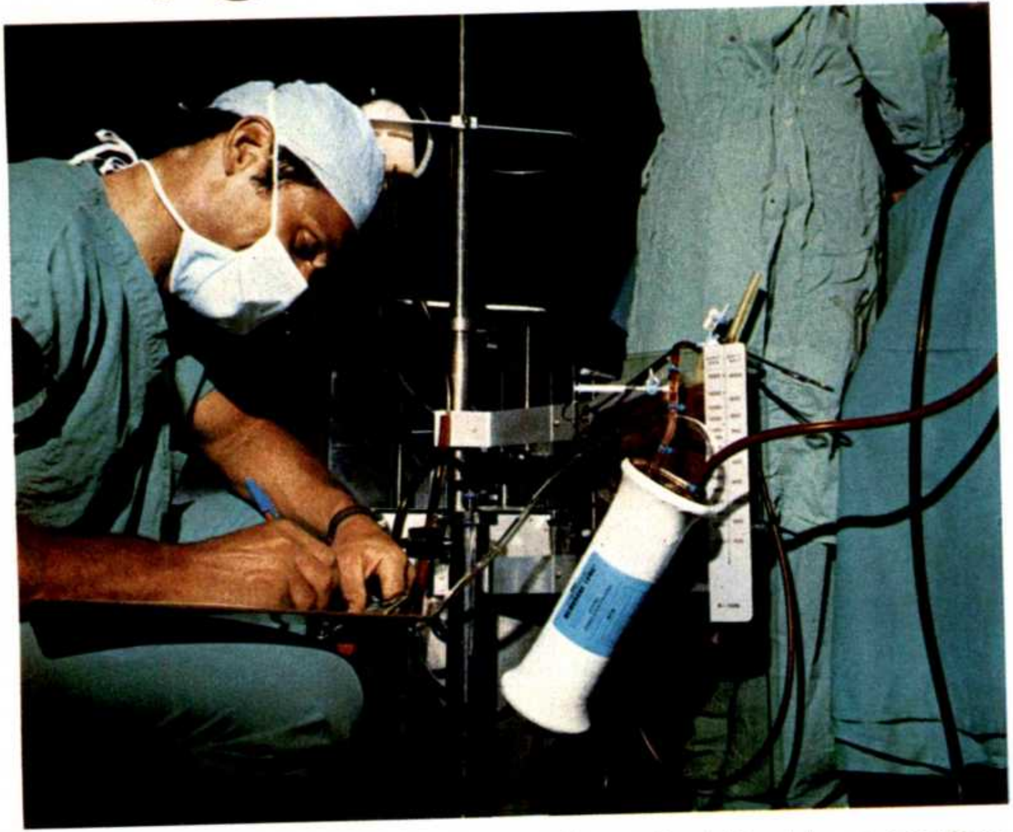

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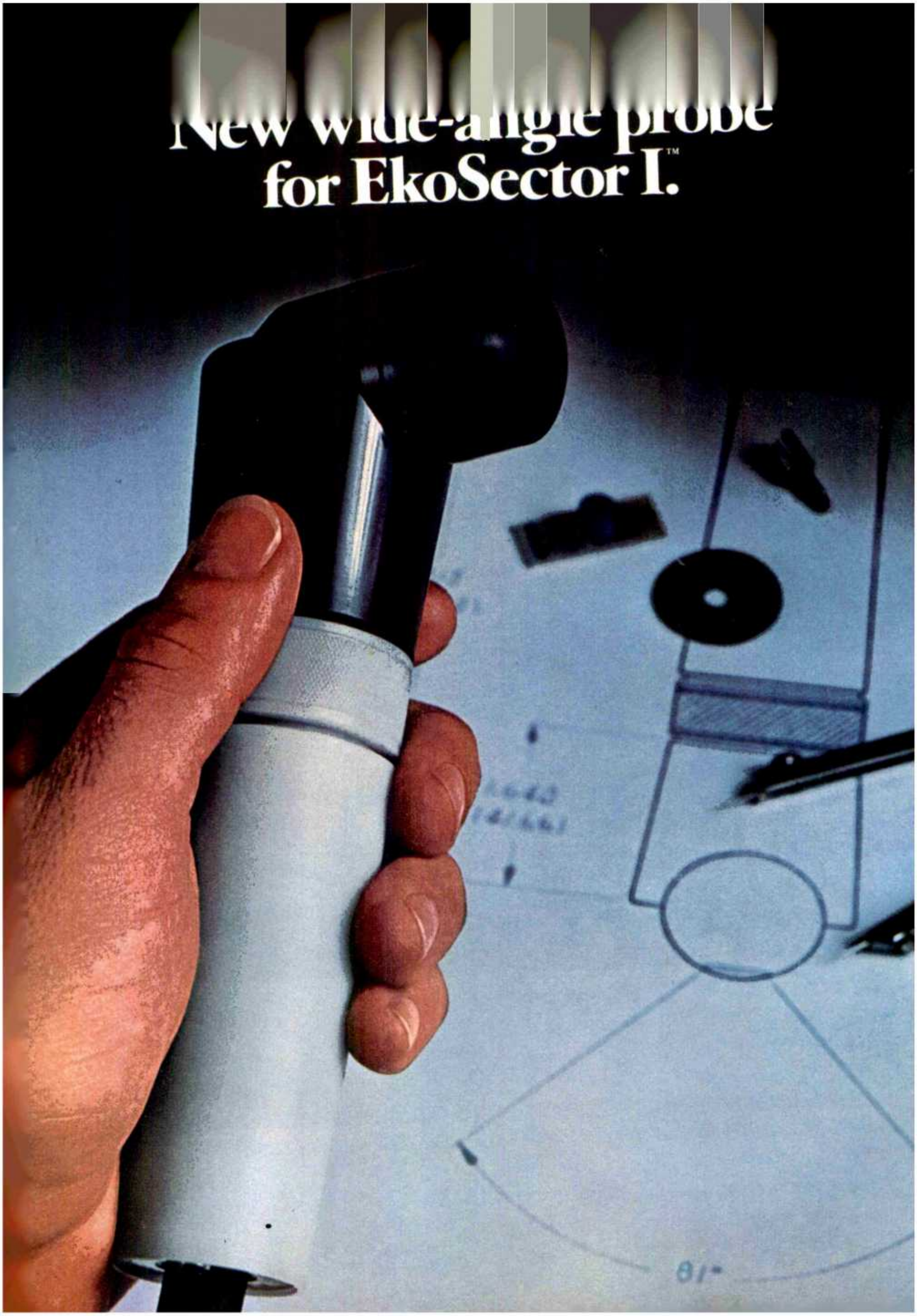
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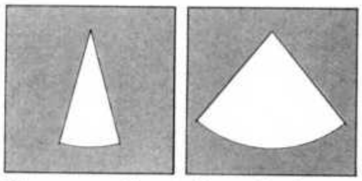

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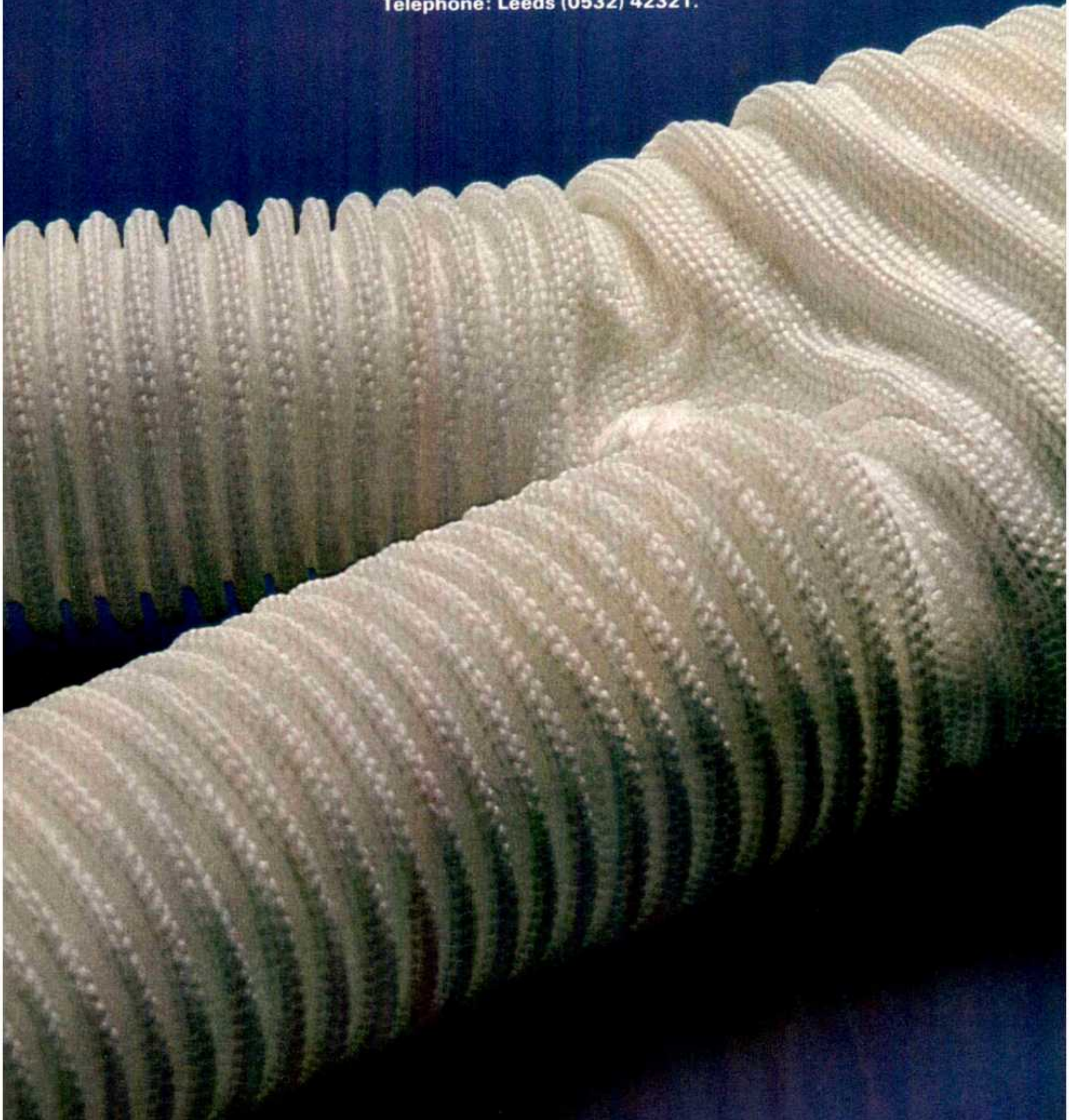

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British Heart Journal, 1978, **40**, 1069-1118

A co-operative trial in the primary prevention of ischaemic heart disease using clofibrate

Report[1] *from the Committee of Principal Investigators*

SUMMARY A double-blind intervention trial was started in 1965 to test the hypothesis that the incidence of ischaemic heart disease in middle-aged men can be reduced by lowering raised serum cholesterol levels. It was carried out in 3 European centres—Edinburgh, Budapest, and Prague. Serum cholesterol was to be lowered by the drug clofibrate (ethyl chlorophenoxyisobutyrate) which was considered to be free from serious side effects.

Studies were carried out on 15 745 males, aged 30 to 59 at entry, for an average of 5·3 years, accumulating 83 534 years of experience. The treatment group, of about 5000, Group I, was a randomly chosen half of the men in the upper third of the serum cholesterol distribution in some 30 000 volunteers. The comparable control group, Group II, comprised the other 5000 men of the upper third of the cholesterol distribution, and these were given a placebo. A further control group, Group III, of 5000 men, was selected randomly from the lower third of the cholesterol distribution. These numbers were chosen in order to be 90 per cent certain of detecting a 30 per cent reduction in the incidence of ischaemic heart disease should this occur. Subjects with manifest heart or other major disease were excluded from the trial. No attempt was made to correct other 'risk factors' for IHD, but their presence was monitored and considered in the analysis. Investigators and participants in the trial were unaware of the groups to which individual men belonged.

A mean reduction of approximately 9 per cent of the initial serum cholesterol levels was achieved in the treatment group (ranging from 7 to 11% in the 3 centres); this was less than the 15 per cent fall expected. In Edinburgh, during treatment, serum triglyceride concentrations in Group I resembled those naturally occurring in Group III.

The incidence of IHD was lower by 20 per cent in the clofibrate group compared with the high cholesterol controls ($P < 0·05$); this fall was confined to *non-fatal* myocardial infarcts which were reduced by 25 per cent. The incidence of *fatal* heart attacks was similar in the 2 high cholesterol groups and there was no significant difference in the incidence of angina. Group III showed substantially lower rates of ischaemic heart disease.

The reduction of myocardial infarction in the clofibrate-treated group was greatest in men with the highest levels, and greatest reduction in serum cholesterol. Men with a substantial reduction of cholesterol concentration, who smoked, and also had above average blood pressure levels showed the most benefit.

The numbers of deaths, and crude mortality rates from all causes in the clofibrate-treated group significantly exceeded those in the high cholesterol control group ($P < 0·05$), though the age-standardised mortality rates did not differ significantly between the 3 groups. The numbers of deaths from 'other

---

[1] *Prepared by—*
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I. Gyarfas, Hungarian Institute of Cardiology, Budapest (G. Lamm: 1966-1974)
K. G. Green, ICI, Macclesfield
J. A. Heady and J. N. Morris, MRC Social Medicine Unit, London
M. F. Oliver, The Royal Infirmary of Edinburgh
T. Strasser, WHO, Geneva (Z. Fejfar: 1966-1973)
Investigators—
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Budapest: M. Czukas, J. Duba, E. Östor
Prague: D. Grafnetter, Z. Hejl
London: J. Cooper
WHO, Geneva: Z. Pisa, K. Uemura Copenhagen: G. Lamm (from 1974)
ICI: J. M. Thorp

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vascular causes' and from 'accidents' as well as IHD were similar in Groups I and II. Excluding these, the excess of deaths in the clofibrate-treated over the high cholesterol control group was 77 *v* 47 ($\mathrm{P} < 0{\cdot}01$). The subgroup with the greatest proportionate excess of deaths is that of conditions related to the liver, the biliary, and intestinal systems, with 19 deaths in Group I *v* 7 in Group II ($\mathrm{P} < 0{\cdot}05$). Deaths from these conditions were commoner, however, in Group III than in Group II (age-standardised rates for the 3 groups being 0·75, 0·17, and 0·65, respectively), and it is possible that Group II had fortuitously *low* rates. The cholecystectomy rate for gall stones was higher in Group I than in Groups II and III ($\mathrm{P} < 0{\cdot}001$).

The results of the trial confirm the basic hypothesis that reduction of high serum cholesterol levels, even in middle-age, can reduce the incidence of IHD. However, the fact that clofibrate increases the incidence of gall stones, and the possibility that it may have even more serious local pathological consequences, indicate that it cannot be recommended as a lipid-lowering drug for community-wide primary prevention of ischaemic heart disease.

By 1965, the association of raised serum lipids, particularly cholesterol, with an increased risk of developing ischaemic heart disease, was well established (e.g. Kannel *et al.*, 1964). Whether raised serum cholesterol actually was causative or, simply, the indication of an underlying metabolic disorder was not known. But on general principles, medical opinion held that it was desirable to reduce serum lipids towards accepted normal levels as far as possible. The means of achieving this were largely based on alterations in diet, and experience at that time suggested that the measures thought necessary were impracticable on any wide scale and were unlikely to be adhered to by most individuals in an affluent society. The possibility of using a cholesterol-lowering drug had been considered but until ethyl chlorophenoxyisobutyrate (later called clofibrate) was introduced (Oliver, 1962; Thorp, 1962; Thorp and Waring, 1962; Symposium on Atromid, 1963) none available satisfied the prerequisites of effectiveness and safety. Clofibrate was known to be capable of reducing plasma concentrations of low density, and very low density, lipoproteins, and thus cholesterol and triglyceride. It was decided, therefore, to initiate a trial in healthy volunteers to find out whether reducing plasma lipids, using clofibrate, would result in a decreased incidence of ischaemic heart disease. No deliberate attempt would be made to change the life style of participants or to rectify other risk factors. A full account of design and procedure has already been published (Heady, 1973). The trial has now been completed, as planned; the present paper summarises the main points of methodology and gives the results.

Trial design—procedure

15 745 healthy men, aged 30-59, selected on the basis of a preliminary determination of serum cholesterol level were assigned to 3 groups as follows: half of the men in the upper third of the distribution of serum cholesterol values were assigned at random to a *clofibrate-treated group* (*Group I*) taking 1·6 g clofibrate daily; the other half of the upper third constituted a *control group* (*Group II*) taking identical capsules containing olive oil. A *second control group* of similar size (*Group III*), chosen at random from the lowest third of the serum cholesterol distribution, also received the olive oil capsules (Fig. 1).

Allocation to the high and low cholesterol groups was carried out every one or two months at each centre, from volunteers 'screened' during the period concerned. Thus, the cut-off levels into thirds varied chronologically.

The essential part of the trial was, thus, the double-blind comparison of the two randomly selected high serum cholesterol groups. The low serum cholesterol group served as a comparison (also double-blind) between men whose untreated cholesterol levels were 'naturally' low and those in Group I whose cholesterol levels fell under treat-

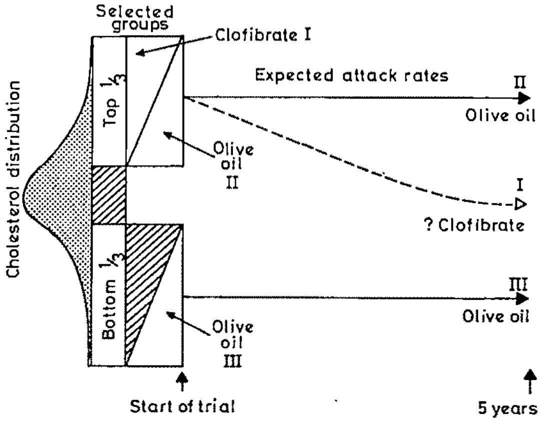

Fig. 1 *Design of the trial (broken line represents hypothetical effect of clofibrate on serum cholesterol and IHD attack rates).*

ment. It also, in fact, served as a useful comparison with the other control group.

The study was designed to last 5 years for each subject admitted and it was assumed that (*a*) 70 per cent of the volunteers would remain in the study for that length of time, and (*b*) the untreated incidence of clinical episodes of coronary heart disease in healthy men aged 30 to 59 with moderately raised serum cholesterol levels would be 1 per cent per annum. The number of volunteers was to be large enough to give a 90 per cent chance ($\beta = 10\%$) of detecting, in the clofibrate treated group, a *reduction of one third* in the incidence of heart attacks compared with the high cholesterol control group, at the 1 per cent level of significance (two-sided). To meet these requirements the study would have to admit at least 15 000 subjects.

The figure of one-third reduction in incidence was chosen because available evidence in the early 1960's suggested that clofibrate might be expected to reduce raised serum cholesterol levels by about 15 per cent and that such a reduction might be associated with a fall in incidence of about 30 per cent. It was also felt that if a reduction of 30 per cent were achieved it would be a reasonable basis for prophylactic treatment, whereas with a smaller reduction the value of such intervention would be more problematical.

The men were recruited in ways which differed in the 3 centres (Heady, 1973) from lists of blood donors, electoral rolls, tuberculosis screening registers, and by advertising among the general public. Recruitment started in 1964 but was not complete until March 1972. After primary selection on the basis of serum cholesterol level, an explanation of the purpose of the study was made to the subject, and those who were willing to participate were medically examined before admission to the trial. The men with high serum cholesterol levels were then randomised to the clofibrate treated and the control group at each centre separately. After admission to the trial men were examined at 6 monthly intervals for 2 years, and thereafter at yearly intervals though they were still contacted by post, or otherwise, at 6-monthly intervals. A final follow-up took place a year after cessation of medication.

The trial was closed down from July 1975 onwards, treatment being withdrawn at the man's next scheduled visit after that date. The process took about one year, so that by the late summer of 1976, no more active treatment was being given.

EXCLUSIONS AND WITHDRAWALS

The *criteria for rejection* at admission on medical grounds are detailed in Appendix 1. They consisted mainly of evidence of previous myocardial infarction; other types of heart disease, arterial hypertension as defined, diabetes mellitus requiring drug therapy, or other diseases with a poor prognosis were also reasons for exclusion. *Criteria for withdrawal* from the trial were similar (Appendix 1) but, of course, included adverse reactions. Because of different practice in the 3 centres, and for obvious ethical reasons, the attendant physicians were allowed latitude in withdrawing subjects from the trial, though this was of course done 'blind'. A history of exercise-induced chest pain was not a reason for withdrawal. At first, hypertension was a firm indication for withdrawal but later this was modified and concurrent antihypertensive therapy was permitted.

FOLLOW-UP PROCEDURE

Medical examination at follow-up was similar to that at entry. Questioning about side effects was general. Specific symptoms were not asked for by name, except indigestion, diarrhoea, and skin reactions, which were known side effects of clofibrate.

Men who gave a positive answer to the standard questionnaire on effort chest pain, and whose resting electrocardiogram was normal, were given a further electrocardiographic examination during and after exercise on a bicycle ergometer.

No systematic advice was given on diet, weight reduction, smoking, or exercise.

Failure to keep an appointment was investigated by the use of 'progress chasers' when necessary. Copies of death certificates were obtained.

All men who withdrew from the trial, or were withdrawn for any reason, medical or non-medical, were considered to be still in the trial for the purpose of calculating exposure-to-risk, up to the date of withdrawal (see Appendix 2). The criteria for classifying events such as death, or ischaemic heart disease, as occurring 'in the trial', or otherwise, are described below, under criteria for assessing the results of the trial.

BIOCHEMICAL MONITORING

Blood was taken for estimation of serum cholestero concentrations at each visit. In Edinburgh, from 1972 onwards, triglycerides were estimated by Auto-Analyzer (Kessler and Lederer, 1965). Urine was examined for sugar and albumin as a routine in Prague and Budapest but not in Edinburgh. Other laboratory tests were carried out as indicated by the history or examination.

DRUG SUPPLIES

Clofibrate for the trial was prepared at Imperial Chemical Industries in opaque white capsules containing 400 mg. The daily dose was 1·6 g. The choice of 400 mg antedated the availability of 500 mg capsules for clinical use. There is no evidence that 1·6 g is less effective than 2·0 g. Control capsules were identical in appearance but, as said, contained 400 mg olive oil. Each pack was labelled with the man's name and trial-number in the pharmacy at each centre.

CONCURRENT MEDICATION

There was no restriction on other drugs, but diabetic patients requiring drug treatment and patients receiving anticoagulants were withdrawn from the trial.

DRUG ADHERENCE

Adherence to treatment was assessed by arranging for the blood which was taken for serum cholesterol estimation to be tested also for the presence of clofibrate (chlorophenoxyisobutyric acid, CPIB). This was done by a semiquantitative method (Barrett and Thorp, 1968) in all the men in the clofibrate treated group at every visit and also in a random 10 per cent of the men in the 2 control groups. The purpose of including the control group was twofold: to make the laboratory assessment 'blind' and to assess the level of prescribing of clofibrate in the general population in each centre. 'Blindness' was arranged by compiling a single list of the trial numbers of all subjects on clofibrate and 10 per cent of the controls arranged in numerical order. The blood samples of the men on this list were routinely examined for the presence of clofibrate, the laboratory staff being aware that some men were not in the treated group but not which men.

RECORDING OF DATA

A standard record was completed on admission, and at each follow-up visit. Events occurring during the trial were notified on a separate form. (Copies of forms are available on request—Addendum A.) After completion at the trial centres, the forms were forwarded to the Medical Research Council's Social Medicine Unit in London, for scrutiny and transfer of the information to computer.

CRITERIA FOR ASSESSING THE RESULTS OF THE TRIAL (See Appendix 3)

(*1*) *Ischaemic heart disease* (*IHD*)

The following *major* end-points were defined:

(*a*) Fatal IHD
- (i) deaths known to have occurred less than 3 hours after onset of symptoms
- (ii) deaths occurring more than 3 hours but less than 28 days after onset.

(*b*) Non-fatal myocardial infarction and acute coronary insufficiently surviving more than 28 days.

(Men who died more than 28 days after onset of symptoms were arbitrarily considered to have had a fresh attack. The death was, therefore, not included as a death in the first attack, or 'in the trial', since men with non-fatal infarctions were withdrawn from the trial. If the death occurred within 1 year of the attack it was included in the total of deaths within 1 year of leaving the trial.)

Additionally, the following *minor* IHD end-points were distinguished:

(*a*) Angina pectoris with abnormal electrocardiogram;
(*b*) Angina pectoris without abnormal electrocardiogram;
(*c*) Abnormal electrocardiogram without chest pain.

(*2*) *Deaths from all causes*

These were subdivided into deaths from IHD and other deaths. In tables of deaths from all causes, deaths occurring within 1 year of leaving the trial have been included.

Definitions of the terms used are given in Appendix 3, as also are those of other events such as 'claudication' which were notified but were not reasons for withdrawal.

A panel of 2 physicians, not concerned with the day-to-day running of the trial, and situated at WHO headquarters in Geneva, reviewed all events that the participating physicians in the centres considered might be due to ischaemic heart disease, as defined.

Deaths or other events, such as IHD, were deemed to have occurred 'out of the trial' if they occurred after a visit at which the subject was excluded on medical grounds or had, himself, 'opted out', that is had stated his intention of not continuing to take the treatment. If, however, the last visit had been one at which neither of these things had happened, a death (or other event) was considered to have occurred 'in the trial' if it occurred within 9 months of the last visit, at the stage in the trial when visits should have occurred at 6-monthly intervals, or within 18 months at the stage when visits should have occurred at yearly intervals. These periods were chosen to coincide with the definitions of a 'missed visit' or 'failure to attend', which, in turn, were related to the supply of pills which a subject would take away with him at an ordinary visit. Events which, after such visits, did not occur within these time limits were considered to have occurred 'out of the trial'. A special attempt was made to trace all deaths occurring within 1 year of leaving the trial, and for the most part, other out-of-trial deaths have not been considered in the analysis.

MONITORING OF RESULTS

The policy was adopted of not reporting results to the investigators so as to avoid influencing their attitude to the trial. The statisticians and an epidemiologist chosen for this purpose alone had access to the results as they came in. The following rules were developed during the study for determining when the main results should be released to the principal investigators:

(*a*) If there were a significant result ($P < 0{\cdot}10$) against the treatment in terms of the main end-points.

(*b*) If there were a significant result ($P < 0{\cdot}10$) against the treatment for any important side effect where useful discussion would be inhibited by lack of knowledge of the main results.

(*c*) If it became clear that the main result could not became significant ($P < 0{\cdot}01$) in favour of the treatment.

(*d*) If there were a significant result ($P < 0{\cdot}01$) in favour of the treatment in terms of the main end-points.

A sequential scheme was used with a power of over 90 per cent to detect a difference of 33 per cent between treated and control at the appropriate levels of significance (Appendix 2).

STANDARDISATION OF PROCEDURES

(*a*) *Blood pressure* was taken in accordance with WHO recommendations (1962). (Observer variability was checked periodically within centres.)

(*b*) *Skinfold thickness* (triceps and subscapular) were measured according to the recommendations of Rose and Blackburn (1968).

(*c*) *Electrocardiograms*, at rest, were recorded on 12-lead electrocardiographs (unipolar chest leads). Exercise electrocardiograms were done under conditions which complied with the World Health Organization criteria (WHO, 1968). Classification of electrocardiogram was by Minnesota Code (Blackburn *et al.*, 1960; Rose and Blackburn, 1968), and was carried out 'blind, that is in ignorance of the subject's treatment group. The case records of all infarctions or deaths attributed to ischaemic heart disease were checked by the panel at WHO, Geneva, mentioned earlier. In case of disagreement between the finding of the centre and that of the WHO panel, the electrocardiogram was reviewed at the annual meeting of the investigators and a committee decision was reached.

To maintain comparability between centres, sets of electrocardiograph recordings were circulated for coding at all centres with satisfactory results.

(*d*) *Serum cholesterol:* different methods of cholesterol estimation were used in each centre. The laboratories were subject to both internal and external quality control.

Internal quality control was mainly by the inclusion of a sample of an internal control pool of frozen lyophilised serum in each analytical day (or run). When pools were renewed there was a period of overlap between the new and old pools.

External quality control was by exchange of samples between centres and also by the participation of each centre, first in the programme in the WHO-CDC International Lipid Standardization Laboratory in Atlanta, USA, and later in that of the European Regional WHO Lipid Reference Centre in Prague, which was itself one of the trial laboratories.

Procedures are available on request (Addendum B).

STATISTICAL METHODS

The details of the statistical methods used are in Appendix 2. This deals with age-standardisation, life-table calculations, the definitions and calculation of cholesterol change and mean in-trial cholesterol levels, and with multivariate analysis. A few points only need to be mentioned here.

Life table calculations were carried out by standard methods. Tests of statistical significance of differences in 'survivorship' use a method, similar to the 'log-rank' method (Mantel, 1966; Breslow, 1975), which compares the survivorship curves as a whole rather than at a single time interval after admission.

Statistical significance: in the tables attention is drawn to significant differences between Groups I and II only. Other significant differences are discussed in the text.

Age-standardisation is not necessary for comparing incidence and mortality rates in Groups I and II since the age-distributions in these 2 randomly allocated groups were almost identical. It is, however, necessary in comparing the rates in Group III with those in Groups I and II because the men in Group III, chosen on the basis of lower serum cholesterol levels, were on average slightly younger than those in Groups I and II.

Age-standardisation is also important in comparing other groups whose age-distributions cannot be *assumed* to be the same, for example those with high or low blood pressure, or smokers and non-smokers. Standardisation was confined to the ages 40 to 59 because the number of events at ages 30 to 39 was small (6% of all incidents of IHD) and

TABLE 1

Characteristics at Entry by Group, All Centres

	Group I	Group II	Group III
	Clofibrate	High Cholesterol Control	Low Cholesterol Control
Number of Men	5331	5296	5118
	Mean Values ± S.E. Mean		
Serum Cholesterol (mg/dl)[a]	249 ± 0.5	247 ± 0.4	181 ± 0.4
Age (years)	45.9 ± 0.1	45.8 ± 0.1	44.2 ± 0.1
Height (cm) (H)	172.6 ± 0.1	172.6 ± 0.1	173.3 ± 0.1
Weight (Kg) (W)	79.4 ± 0.1	79.7 ± 0.2	77.1 ± 0.2
Quetelet Index ($\frac{W}{H^2}$ X 10,000)	26.6 ± 0.04	26.7 ± 0.05	25.6 ± 0.05
Systolic blood pressure (mmHg)	135.4 ± 0.2	135.2 ± 0.2	131.7 ± 0.2
Diastolic blood pressure (mmHg)	87.1 ± 0.1	87.2 ± 0.1	84.9 ± 0.1
Skinfold: Triceps (mm)	12.7 ± 0.1	12.8 ± 0.1	11.6 ± 0.1
Subscapular (mm)	18.5 ± 0.1	18.5 ± 0.1	16.4 ± 0.1
	Percentage with Characteristic		
	%	%	%
Age(yrs) 30-	16	17	27
40-	56	55	50
50-	28	27	23
Never Smoked	25	25	33
Ex-smokers	18	18	17
Smokers (cigarettes or other)	56	56	51
Smokers (20+ cigarettes/day)	44	43	36
Father dead	74	73	68
Mother dead	49	49	45
Married	89	90	88
Positive questionnaire for angina(b)	2.1	1.7	1.4
Positive questionnaire for leg pain(b)	1.3	1.3	0.6
Basal murmur	7.6	7.6	6.2
Apical murmur	8.4	7.7	8.8
Arcus	13	12	6.4
Xanthelasma	3.4	2.9	2.2
Xanthoma tuberosum	0.2	0.1	0.1
Xanthoma tendinosum	0	0	0.1
ECG abnormality (Minnesota Code 4-2 or 5-2)	0.8	1.0	0.8

(a) Mean of pre-treatment serum cholesterol values corrected for Centre differences. See Appendix 2.

(b) A modified version of the London School of Hygiene Cardiovascular Questionnaire, Rose & Blackburn 1968. (Addendum A).

might produce spurious results, and, also, because there were virtually no men in Prague under the age of 40. For the particular purpose of comparing rates *between* centres standardisation was restricted to the age-range 40 to 54 because there were also very few men aged 55 or over in Prague. Equal weightings were given to each 5-year age-group in the standardisation, for simplicity, and because, as it happened, in each centre, the number of men in each of the 4 age-groups, from 40 to 59, in the general population was not very different.

Results

Results are presented in the main part of this report for the 3 centres combined, though attention is drawn to important differences between centres. The main results for IHD for the separate centres individually are shown in Appendix 4 and additional inter-centre differences are available in Addendum C.

COMPARABILITY OF GROUPS

Table 1 shows the characteristics recorded at entry to the trial, for all 3 centres combined, for each Group. There were no important differences between Groups I and II, the high serum cholesterol groups, in any of these characteristics; and this was true also within each centre. Group III, selected on the basis of lower serum cholesterol levels, did however show differences from the other 2 groups. On average, the men in this group were younger, lighter, taller, had lower blood pressures, and smoked less.

There was an important difference between centres in age-distribution of the subjects (Addendum D). In Prague virtually no subjects were recruited under the age of 40, whereas one third of those in Edinburgh and one quarter of the Budapest men were under that age. Budapest, at 32 per cent, had the highest proportion of men over 50 compared with 21 per cent in Edinburgh, and 24 per cent in Prague. Only 57 men in Prague were aged 55 or more. For the trial as a whole, more than half of the subjects were aged between 40 and 50.

MEN AND MAN-YEARS IN TRIAL

Table 2 shows the numbers of men who entered, and completed, or failed to continue in the trial for various reasons. Some 300 had in fact been in the trial for as many as 8 years when it closed. On the other hand, 227 late entrants did not have the opportunity to complete 5 years before it ended. Subtracting these from the total admitted, 69 per cent of those for whom it was possible remained in the trial for 5 years, slightly less than the 70 per cent allowed for in the planning stage. The percentage of men who left the study for any reason was 13 per cent in the first year, and about 5 per cent annually thereafter; the 3 centres behaved similarly.

An attempt was made to establish whether those who 'defaulted' or who were excluded for medical reasons, and those who were in the trial at the end of the study were alive or dead 1 year after leaving the trial. This information was available for 99 per cent of all the men in the trial.

The numbers of men admitted to the trial and the numbers of man-years they experienced in the trial for each centre and each 5-year group of age at admission are available on request (Addendum D).

DRUG ADHERENCE

Group I

In Budapest, 98 per cent of men who were in the trial for at least 5 years showed positive readings on all but 2 occasions and 94 per cent on all but 1 occasion. The corresponding figures for Prague were 94 and 85 per cent. For Edinburgh, during the first 4 years of the trial, the figure was 95 per cent on all but 1 occasion.

Average concentrations of clofibrate in the blood of those men with positive readings in the clofibrate treated group are shown in Appendix 5 (i).

Groups II and III

In Budapest, 1 per cent of men who were in the trial for at least 5 years showed positive readings on more than 1 occasion. In Prague, 19 per cent showed positive readings on more than 1 occasion and 5 per cent on more than 2 occasions. In Edinburgh, 4 per cent showed positive readings on more than 1 occasion. No explanation is available for the higher proportion of positive readings in Prague.

Incidence of IHD and mortality from all causes

Comparing the clofibrate-treated group with the high cholesterol control group the 3 main results of the study are:

(*a*) the overall incidence of major IHD was significantly lower in the clofibrate-treated group;

(*b*) this difference was confined to non-fatal myocardial infarction;

(*c*) total mortality from all causes was significantly higher in the clofibrate-treated group.

Details of these findings are given below, those relating to the incidence and mortality from IHD first, and the mortality from other causes later.

TABLE 2

Numbers of Men at Different Stages

Total Number of Men Screened	52,519
Number of Men invited to attend on basis of their serum cholesterol level	26,259 (a)
Number Rejected for Medical Reasons	725
Number of Men who did not attend for Entry	9,789
Number of Men admitted to Trial	15,745

	Group I Clofibrate	Group II High Cholesterol Control	Group III Low Cholesterol Control	All Groups
Admitted to Trial	5,331	5,296	5,118	15,745
Of these:-				
Withdrawn after entry for medical reasons (including deaths and myocardial infarction)	588	582	390	1,560
Failed to continue for other reasons	1,246	1,188	1,256	3,690
In the Trial when it ended	3,497	3,526	3,472	10,495
Number who completed 5 years	3,586	3,608	3,509	10,703

(a) Half those otherwise eligible were excluded because of the cholesterol levels found at the preliminary screening. (See text and Figure 1).

INCIDENCE AND MORTALITY FROM MAJOR IHD

Table 3 shows the incidence of the first episodes of major IHD in each Group according to the age of the subject at entry to the trial, and distinguishes between fatal and non-fatal attacks. Data for deaths within 3 hours of onset of symptoms are given separately. Rates are standardised at ages 40 to 59.

The *overall incidence of major IHD* (first clinical episodes) in the clofibrate-treated group (5·9 per thousand per annum) was 20 per cent lower than the incidence in the high cholesterol control group (7·4) ($P < 0{\cdot}05$).

The *mortality from IHD* in first episodes, on the other hand, was virtually the same in the 2 groups (1·3 and 1·2) and, hence, the difference between the 2 groups lies in *non-fatal myocardial infarcts* (4·6 and 6·2 per thousand) ($P < 0{\cdot}05$).

The incidence of both fatal and non-fatal major IHD events was significantly less in Group III, the low cholesterol control, than in either of the 2 high cholesterol groups ($P < 0{\cdot}01$ for non-fatal and $< 0{\cdot}05$ for fatal, age-standardised).

Deaths known to have occurred less than 3 hours from the onset of symptoms were more common (23), though not significantly so, in Group I than in Group II (17). Again, the numbers in Group III were much smaller (8).

The same information (except for sudden deaths) is shown diagrammatically in Fig. 2 on a life-table

TABLE 3

Incidence of Major Ischaemic Heart Disease (IHD), Non-fatal and Fatal, by Age at Entry

Rates per 1000 per annum

Event	Age at Entry (years)	Group I Clofibrate		Group II High Cholesterol Control		Group III Low Cholesterol Control	
		No.	Rate	No.	Rate	No.	Rate
All Major IHD	30-	3	1.8	3	1.8	2	0.6
	35-	8	3.0	7	2.3	3	0.8
	40-	19	3.0	31	5.0	8	1.4
	45-	61	6.3	84	8.7	18	2.2
	50-	44	8.8	53	10.4	22	4.9
	55-	32	11.5	30	11.6	9	4.6
	Total	167*	5.9*	208*	7.4*	62	2.3
	St.40-59 (a)		7.4		8.9		3.3
Non-Fatal Myocardial Infarction	30-	2	1.2	3	1.8	2	0.6
	35-	6	2.2	7	2.3	1	0.3
	40-	16	2.5	28	4.6	4	0.7
	45-	48	4.9	72	7.5	14	1.7
	50-	35	7.0	42	8.2	18	4.0
	55-	24	8.6	22	8.5	7	3.6
	Total (b)	131*	4.6*	174*	6.2*	46	1.7
	St.40-59		5.8		7.2		2.5
Fatal IHD	30-	1	0.6	0	0.0	0	0.0
	35-	2	0.7	0	0.0	2	0.6
	40-	3	0.5	3	0.5	4	0.7
	45-	13	1.3	12	1.2	4	0.5
	50-	9	1.8	11	2.2	4	0.9
	55-	8	2.9	8	3.1	2	1.0
	Total	36	1.3	34	1.2	16	0.6
	St.40-59		1.6		1.8		0.8
Of these: Deaths within 3 hours (c)		23	0.8	17	0.6	8	0.3

(a) Standardised rates for the four age-groups 40-44, 45-59, 50-54, 55-59, equal weights being given to each age-group.

(b) Includes 38 with Acute Coronary Insufficiency (Intermediate Coronary Syndrome), 18, 16 and 4 in Groups I, II and III respectively.

(c) The numbers of IHD deaths occurring from 3-12 hours were 4, 6, 3, in the three groups respectively.

* Significant difference between Groups I and II ($P < .05$).

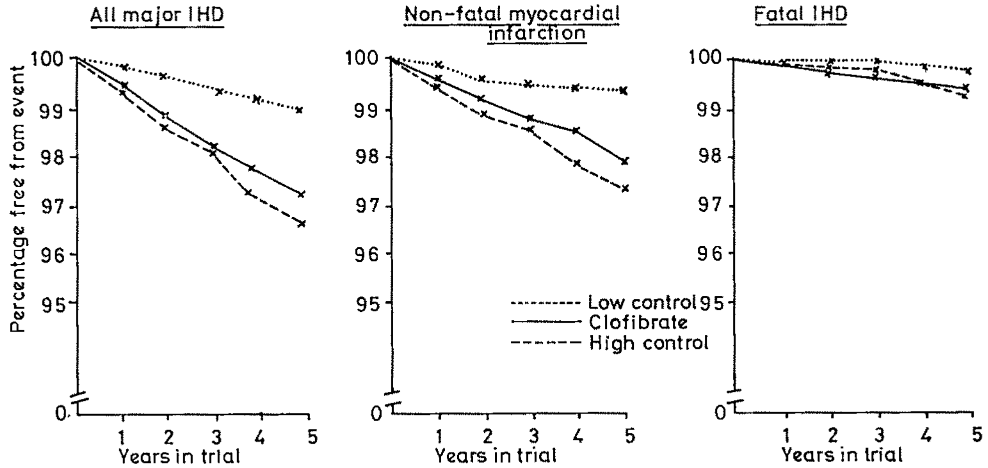

Fig. 2 *Major ischaemic heart disease in the first 5 years (calculated on a life-table basis).*

basis, that is showing the proportions free of IHD at various periods after entry to the trial. The significance tests based on this form of analysis, which take into account the shape of the whole curve, give similar results to those given above based on the comparison of overall rates, that is a significant (P < 0·05) reduction in non-fatal myocardial infarction in Group I compared with Group II. The diagram itself shows results up to 5 years only, because after that stage rates are based on very small numbers and diagrammatic representation would be misleading. It would be unwise to interpret the apparently greater divergence at 3 years of the curves for the clofibrate and high cholesterol groups as showing that 3 years of treatment has some critical importance. It is more likely to be a random fluctuation. Details of the life-table analysis and of the method used are shown in Appendix 2.

Figure 3 shows the standardised rate *for each centre*, by Group, for all major IHD, for fatal IHD, and for non-fatal myocardial infarction. For the reasons stated above, standardisation is at ages 40 to 54, not 40 to 59. At each centre the rates for all IHD, and for non-fatal myocardial infarction, were higher in Group II than in Group I, and the rates in both Groups were higher than those in Group III. There was no consistent pattern for fatal IHD in the centres, but the numbers of deaths were small.

The incidence of major IHD (taking all groups together) was significantly lower (P < 0·01) in Budapest than in either of the other 2 centres. Details of numbers and rates are shown in Appendix 4.

In order to test whether adherence to treatment had any important influence on the main result (that is whether, for instance, the difference betwee the clofibrate-treated group and the high choles terol control group in the number of major IH events might have been greater if the treatment ha been more strictly observed in Group I than it was the proportion of negative estimates of chlorophen oxyisobutyric acid (CPIB) in the blood was calcu lated for the men in Group I who had such an even and compared with the same proportion in all men i Group I. A further test was made, in Group I, o adherence to treatment at the last visit before a IHD event compared with visits at the same stage i the study for all men. The results are shown i Appendix 5 (ii) and (iii). There seems to be n

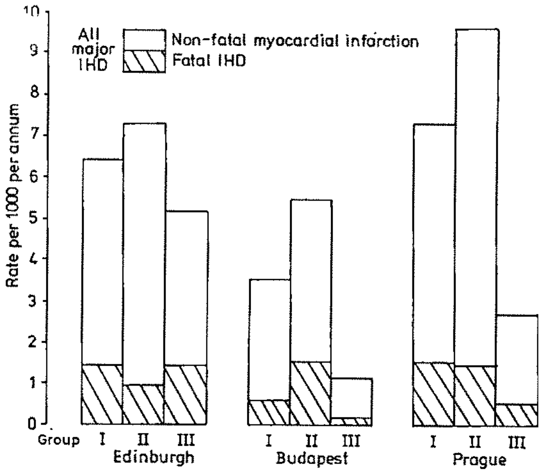

Fig. 3 *Age-standardised incidence and mortality rates of major IHD, 40 to 54 years, per 1000 per annum by centre.*

TABLE 4

Incidence of Minor Ischaemic Heart Disease

Rates per 1000 per annum

Condition(a) (newly arising in the trial)	Group I			Group II			Group III		
	Clofibrate			High Cholesterol Control			Low Cholesterol Control		
	No.(b)	Rate	Age-St. Rate	No.(b)	Rate	Age-St. Rate	No.(b)	Rate	Age-St. Rate
Angina Pectoris with abnormal ECG (c)	60	2.1	2.6	48	1.7	2.4	31	1.1	1.4
Angina Pectoris without abnormal ECG (d)	212	7.4	9.0	226	8.0	9.6	181	6.7	8.4
Abnormal ECG without chest pain (c)	223	7.9	9.1	260	9.3	10.6	176	6.5	8.8

(a) For definitions see Appendix 3.

(b) Numbers and crude rates relate to men aged 30-59. Age-standardised rates relate to men aged 40-59.

(c) Abnormal ECG = Minnesota Codes: 4.1, 4.2, 5.1, 5.2, 6.1, 6.2, 7.1, 8.3, 11.1, 12.1, 14.1.

(d) As defined by angina questionnaire. (Addendum A).

TABLE 5

Other Vascular Events and Diabetes: Incidence and Withdrawals

Rates per 1000 per annum

Condition(a) (newly arising in the trial)	INCIDENCE									WITHDRAWALS		
	Group I			Group II			Group III			I	II	III
	Clofibrate			High Cholesterol Control			Low Cholesterol Control			Clof.	H.C.C.	L.C.C.
	No.(b)	Rate	Age St.Rate	No.(b)	Rate	Age St.Rate	No.(b)	Rate	Age St.Rate	No.	No.	No.
Vascular Conditions												
Cardiac Arrhythmia (c)	173	6.1	7.5	166	5.9	6.7	152	5.6	8.1	1	1	0
Hypertension (as defined)	192*	6.8*	7.5*	242*	8.6*	9.9*	146	5.4	6.3	63**	96**	60
Other Heart Disease(d)	-	-	-	-	-	-	-	-	-	9	9	11
Non-fatal Cerebrovascular disease	18	0.6	0.9	13	0.5	0.8	14	0.5	1.0	5	1	2
Intermittent Claudication(e)	184	6.5	7.5	184	6.5	8.3	108	4.0	4.8	43	30(f)	16(f)
Venous Thrombosis & Embolism(d)	-	-	-	-	-	-	-	-	-	7	2	1
Diabetes (as defined in each centre)	129	4.6	5.1	102	3.6	4.0	67	2.5	3.4	47*	26*	18

(a) For definitions see Appendix 3.

(b) The numbers and rates relate to men aged 30-59. The age standardised rates relate to men aged 40-59.

(c) Minnesota code 8-1, 8-3.

(d) Incidence figures are not available because these conditions were not notifiable.

(e) As defined by intermittent claudication questionnaire. (Addendum A).

(f) In Edinburgh 6 men in Group II and 3 men in Group III with confirmed peripheral artery disease were not withdrawn from the study. (See text.)

* Significant difference between Groups I and II ($P < 0.05$).

** " " " Groups I and II ($P < 0.01$).

consistent difference between the CPIB values of men who developed events compared with all men.

INCIDENCE OF MINOR IHD

Table 4 shows the number of minor IHD events in each group together with incidence rates, both crude, for all ages, 30 to 59, and standardised at ages 40 to 59. Minor IHD is classified as angina pectoris with and without abnormal electrocardiogram and as an electrocardiographic abnormality without chest pain, as defined earlier under 'criteria for assessing the results of the trial'. There was no significant difference between Groups I and II in angina pectoris with or without abnormal electrocardiogram, or in those with electrocardiographic abnormalities in the absence of chest pain. The major items of the Minnesota code (4-1, 5-1, 7-1, and 11-1) were analysed separately and together, and again no difference was found between Groups I and II.

OTHER VASCULAR EVENTS AND DIABETES

Table 5 shows the result for other vascular events and diabetes, and includes withdrawals from the trial, as well as incidence.

Apart from hypertension and diabetes there were no significant differences in these conditions between Groups I and II.

Hypertension is defined for the purposes of this trial as a diastolic pressure of 120 mmHg or more on one occasion, between 110 and 119 mmHg more than once, or once only if specific electrocardiographic abnormalities were present (Appendix 3). The incidence and rate of withdrawal in Group I was significantly lower than in Group II. The incidence in Group I was lower than Group II in each centre.

In spite of this, however, mean blood pressure for all subjects during the trial was not materially different in Groups I and II as shown in Table 6 (i). Thus, clofibrate appeared to show no appreciable blood pressure lowering effect overall.

Table 6 (ii) shows that mean blood pressure at the visit immediately before a major event was higher than the mean pressure in men, at the same stage in the trial, who did not have such an event. This was equally true for Groups I and II.

The incidence of hypertension in Group III was significantly lower than in Groups I or II (Table 5) and higher in Prague than in either of the other two centres (Addendum C).

Diabetes was notified more frequently in Group I than in Group II. Though this difference was not statistically significant the number of withdrawals for diabetes requiring drug treatment was significantly higher in Group I than in Group II. Diabetes was much more frequently notified in Prague than in the other centres and, indeed, accounted for more than half the number in the whole trial (Addendum C).

Peripheral artery disease was not a specified reason for withdrawal. Ischaemic leg pain, identified by

TABLE 6

Mean Blood Pressure (mmHg)

		Group	At Entry	Years in Trial				
				1	2	3	4	5
(i) All Men	Mean Systolic Blood Pressure	I Clofibrate	135	132	131	133	133	134
		II High Cholesterol Control	135	132	131	133	134	134
	Mean Diastolic Blood Pressure	I Clofibrate	87	84	83	84	83	84
		II High Cholesterol Control	87	85	84	85	85	84
(ii) Men with a major I.H.D. event (value at visit immediately preceding I.H.D. event)								
	Mean Systolic Blood Pressure	I Clofibrate	148	141	139	144	140	137
		II High Cholesterol Control	144	142	140	143	136	149
	Mean Diastolic Blood Pressure	I Clofibrate	89	88	89	86	85	87
		II High Cholesterol Control	88	88	88	90	86	92
Men who did not have a major I.H.D. event	Mean Systolic Blood Pressure	I Clofibrate	135	131	131	133	133	134
		II High Cholesterol Control	135	132	131	133	134	134
	Mean Diastolic Blood Pressure	I Clofibrate	87	84	83	84	83	84
		II High Cholesterol Control	87	85	84	85	85	84

questionnaire (Addendum A), was notifiable to the controlling centre in London. In 1971 notifications in Group I had reached a number which was significantly higher than in Group II (though, as Table 5 shows, the numbers were finally exactly equal) and a special investigation was set up to assess the situation. All cases reported as having ischaemic leg pain were examined by a vascular specialist at each centre, who was unaware of group identity. Blood flow measurements were carried out on doubtful cases. 'Confirmed' cases of peripheral artery disease were withdrawn from the trial and these are the figures shown in Table 5. The difference between Groups I and II is not statistically significant. At Edinburgh the numbers confirmed were small and it was decided to withdraw from the trial only the 6 patients receiving clofibrate. (This was possible without disclosing to the physicians running the clinics the identity of the cases 'confirmed' in the 2 placebo groups.) In comparing Groups I and II in Table 5 this should be borne in mind.

Since 1971, the presence or absence of peripheral arterial pulses was notified to London. The numbers of men, in all centres, with at least one absent pulse

TABLE 7

Serum Cholesterol (mg/dl)

Mean Values during the Trial

Centre & Group	No. of men(c)	Screening Visit(s)	Entry Visit	No. of years after entry 1	2	3	4	5	6	7
Edinburgh										
I Clofibrate	1631	249	242	214	214	220	225	227	229	233
II High Cholesterol Control	1658	249	242	241	240	248	252	255	257	259
III Low Cholesterol Control	1646	179	188	187	190	195	200	204	205	208
Budapest(a)										
I Clofibrate	1193	267	256	228	232	236	228	234	244	243
II High Cholesterol Control	1146	264	255	244	251	254	246	251	257	250
III Low Cholesterol Control	1179	189	194	187	193	197	195	199	201	197
Prague										
I Clofibrate	1884	290	287	255	257	260	262	259	260	264
II High Cholesterol Control	1880	286	282	280	277	279	280	278	275	279
III Low Cholesterol Control	1667	204	205	213	216	217	218	214	214	217
Cholesterol Decrease(b) in the Clofibrate-treated Group relative to the High Cholesterol Control Group expressed as a percentage of starting values		Edinburgh		11.1	10.7	11.5	11.2	11.2	11.6	10.7
		Budapest		6.6	8.0	7.5	7.7	7.0	5.9	3.5
		Prague		10.3	8.7	7.8	7.8	8.1	6.7	6.6
		All Centres(d)		9.7	9.1	9.0	8.9	8.8	8.2	9.0

(a) Throughout this Report, Budapest cholesterol figures refer only to men admitted on the basis of the Watson method of cholesterol estimation. (Addendum B).

(b) Decrease is measured in each Group from the mean pre-treatment levels, i.e. the levels at the Screening Visit(s) and at Entry Visit.

(c) Men who had cholesterol values at screening and entry visits.

(d) Adjusted for differences between Centres, see Appendix 2.

on at least one occasion were: Group I: 257; Group II: 309; Group III: 196 and, with at least two on any occasion: 155, 192, and 114 respectively. The figures for Group III are significantly lower than for Groups I and II ($P < 0{\cdot}01$), as might be expected. The differences between Groups I and II are also significant ($P < 0{\cdot}05$).

CHANGE IN SERUM CHOLESTEROL LEVELS DURING THE STUDY

Table 7 shows the mean serum cholesterol levels at screening and at each trial visit for the men in each Group in each centre. The mean starting levels (both at screening and at first visit) are different in the 3 centres and, in particular, the values are somewhat higher in Prague. The greater part of this excess has been shown by tests of control samples (or by the reference system used) to be the result of the methods of cholesterol determination (Addendum B), so that the actual average cholesterol levels before treatment differed little, in fact, between the 3 centres.

There were considerable variations from visit to visit in the mean levels of cholesterol in all groups during the study, particularly in Edinburgh and Budapest. Whatever the reasons for these variations, in the clofibrate-treated group they were, of course, operative in addition to the effects of the drug. To allow for this, when assessing change from mean pretreatment level, at any stage during the trial, the change seen in the high cholesterol control group was deducted from the change seen in the clofibrate-treated group (Appendix 2). This adjusted figure for Group I, therefore, represents that part of the evident change which could, presumptively, be attributed to clofibrate.

The adjusted figures for change in Group I are shown in the lower section of Table 7 for each centre in each year after entry: they are expressed as a percentage of the mean pretreatment levels. The change remains fairly steady after the initial fall measured at the first follow-up visit (that is 6 months) in each centre. In Edinburgh a decrease of about 11 per cent, in Budapest of about 7 per cent, and in Prague of about 8 per cent was maintained; an adjusted figure for all centres is also presented which varies from 9·7 to 8·2 per cent. These figures fell short of the 15 per cent reduction in serum cholesterol envisaged at the outset of the trial.

INCIDENCE OF IHD IN RELATION TO CHOLESTEROL CHANGE

The relation between incidence of IHD and change in serum cholesterol levels can be studied in 2 ways: by comparing the experience of Group I, where the mean serum cholesterol level was reduced by treatment, with that of the 2 control groups, and by relating the individual change in serum cholesterol levels to incidence.

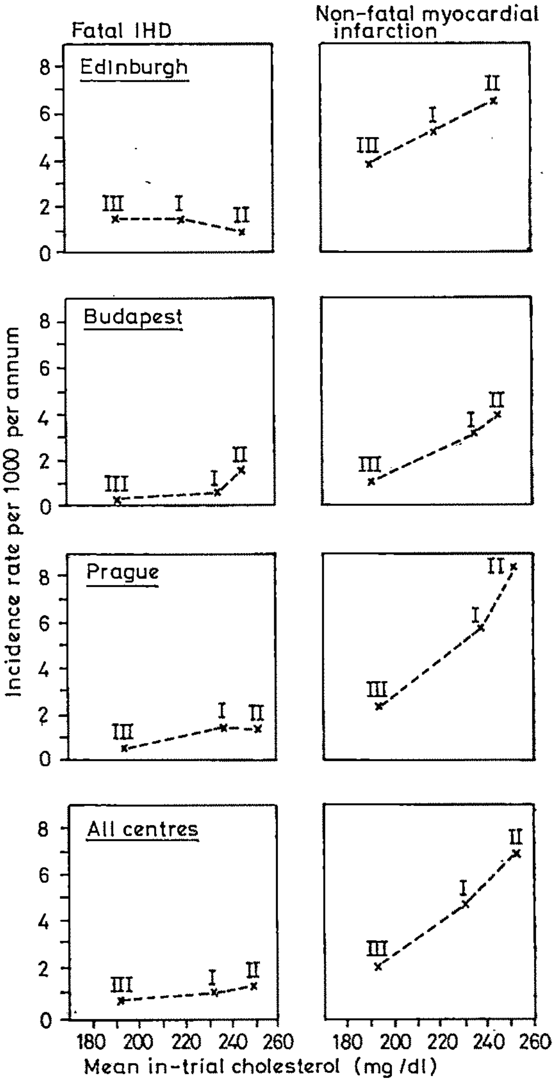

Fig. 4 *Incidence of major ischaemic heart disease and mean in-trial cholesterol by centre and group. Age-standardised rates per 1000 per annum at ages 40-54.*

Incidence related to group changes in cholesterol

The first approach is illustrated in Fig. 4 where the 'mean in-trial cholesterol level' for each Group is related to the age-standardised incidence of IHD, at ages 40 to 54, in that Group. This was done for each centre, and separately for fatal and non-fatal IHD. (Again, this age-range was chosen because centre comparisons are involved.) The derivation of 'mean in-trial cholesterol level' is described in Appendix 2. It allows for variations from visit to visit in mean cholesterol levels, averages the levels over all visits, and takes account of differences between centres in mean levels. For non-fatal myocardial infarction the point for Group I in each centre lies somewhat below the straight line between the points for Groups II and III. The results are not inconsistent with the possibility of some fairly simple one-to-one relation. The results for fatal IHD are less consistent, possibly because of small numbers of events.

Incidence related to individual changes in cholesterol

For the second approach, individual cholesterol change is defined in an analogous way to group change, that is the change in an individual's pretreatment cholesterol levels is adjusted by subtracting from it the change in the mean level of cholesterol of all the men in Group II at the same centre and at the same visit. The mean change for an individual is then calculated as the mean of all changes for that individual from his second visit to his last visit: this can be expressed in absolute terms, or as a percentage of starting values. If a man did not have a second visit, that is he left the trial for any reason before then, it was not possible to calculate a change figure for him. This applies, in particular, to those men who had a heart attack in their first 6 months in the trial, and they are therefore excluded from this analysis.

Because men with the greatest reduction have, on average, the highest initial cholesterol levels and, therefore, are initially at higher risk of heart attack than the men with less reduction, it is necessary to study the relation between cholesterol change and the incidence of IHD within broadly similar levels of starting cholesterol.

In Table 8 the men in each of the 2 high cholesterol groups are classified simply (i) into those with a fall in mean cholesterol and those without, and (ii) into those whose initial pretreatment cholesterol was above or below the median of the distribution of pretreatment cholesterol levels. Since these men are all drawn from the highest third of the overall distribution of starting cholesterols, the figures refer to men in the two highest sixths of that distribution. The median was calculated separately in each centre because of the differences between centres in overall levels.

Table 8 is divided into three parts: 8(i), 8(ii), 8(iii), dealing respectively with all major IHD, non-fatal myocardial infarction, and fatal IHD. In each cell there are 3 numbers: the number of events, the rate per thousand per annum (at all ages and unstandardised), and an 'expected' rate. This expected rate, also expressed per thousand per annum, is calculated from a multivariate analysis (see later) and takes into account the 5 factors which were measured at the start of the trial and were shown to have an independent effect on the subsequent incidence of major IHD—namely, age, initial cholesterol level, smoking, systolic blood pressure, and whether the man's father was alive at the start of the trial—and represents the rate of incidence which would be expected in a group of men in Group II whose ages, initial cholesterol levels, etc., were the same as those of the men who are actually included in the relevant cell of the table. Thus any difference between the observed rate and the expected rate in each cell represents, apart from sampling fluctuations, the effect of cholesterol change—that is a rise or fall in mean cholesterol during the trial whether due to clofibrate or not, and is better evidence than that of the crude rate which, of course, makes no allowance for the fact that the men in the different cells of the table almost certainly have different inherent risks because they are of different ages, have different initial cholesterol levels, etc.

The table shows, first, that, both for fatal and non-fatal infarction, the observed rates were higher in the men whose pretreatment cholesterol concentrations were above the median than in the men with values below the median, and the same is true for the expected rates.

Secondly, in terms of cholesterol change during the trial, the observed rates of major IHD for the men in Group I whose cholesterol fell during the trial were substantially below the expected rates whether their pretreatment cholesterols were low or high. Whereas, for the corresponding men in Group II, the difference between observed and expected was neither so clear nor so consistent. For men in both Groups whose cholesterol levels rose during the trial, on the other hand, the observed rates were higher than the expected. The pattern is similar but not quite so clear for non-fatal myocardial infarction alone, while for fatal IHD the picture is not clear.

Although the differences referred to above are not all individually statistically significant, they are consistent with the suggestion that most of the reduction of non-fatal myocardial infarction in the clofibrate treated Group is associated with reduction of cholesterol concentrations.

Effect of other 'risk factors' on the incidence of major IHD

Before proceeding to the multivariate analysis, Table 9 shows how incidence of major IHD is

TABLE 8

Incidence of Ischaemic Heart Disease by Mean Pre-treatment Cholesterol and Mean Cholesterol Change

Rates per 1000, per annum

(i) Incidence of Major IHD, Fatal and Non-fatal

Mean Pre-treatment Cholesterol(a)		Group I Clofibrate		Group II High Cholesterol Control	
		Fall in Cholesterol	Rise in Cholesterol	Fall in Cholesterol	Rise in Cholesterol
Below Median(b)	Observed Rate	3.7	7.3	6.5	6.1
	Expected Rate(c)	6.2	6.7	6.4	5.9
	No.	37	18	35	43
Above Median	Observed Rate	6.4	12.6	7.6	11.2
	Expected Rate	9.4	11.4	9.2	8.8
	No.	73	14	61	47

(ii) Incidence of Non-fatal Myocardial Infarction

Below Median	Observed Rate	2.7	6.1	6.1	5.1
	Expected Rate	5.3	5.8	5.5	5.1
	No.	27	15	33	36
Above Median	Observed Rate	5.3	8.1	6.0	9.5
	Expected Rate	7.7	9.5	7.6	7.5
	No.	60	9	48	40

(iii) Incidence of Fatal IHD

Below Median	Observed Rate	1.0	1.2	0.4	1.0
	Expected Rate	0.9	0.9	0.9	0.8
	No.	10	3	2	7
Above Median	Observed Rate	1.1	4.5	1.6	1.7
	Expected Rate	1.7	1.9	1.6	1.3
	No.	13	5	13	7

(a) Corrected mean pre-treatment cholesterol (See Appendix 2).

(b) Median values were determined separately for each group and for each centre.

(c) See text.

The following table indicates the mean change in serum cholesterol for all men where a change could be calculated, together with the number of such men in each category

Mean Pre-treatment Cholesterol		Group I Clofibrate			Group II High Cholesterol Control		
		Fall	Rise	Total	Fall	Rise	Total
Below Median	Mean change %	-10.2	6.2	-6.7	-6.2	7.4	1.5
	No. of men	1739	479	2218	976	1281	2257
Above Median	Mean change %	-13.6	5.7	-11.6	-7.7	5.5	-3.0
	No. of men	2027	231	2258	1427	779	2206

TABLE 9

Incidence of Major Ischaemic Heart Disease by Factors Present at Entry

All Centres, Age-standardised Rates per 1000 per annum at ages 40-59

(Rates in brackets are based on fewer than 10 events)

Factor	Group I	Group II	Group III
	Clofibrate	High Cholesterol Control	Low Cholesterol Control
Serum Cholesterol			
Below Median (a)	5.9	8.4	3.3
Above Median	9.7	11.1	3.6
Systolic Blood Pressure (mmHg)			
Under 120	5.8	4.9	(2.7)
120-139	7.6	7.3	2.5
140-159	7.5	12.6	4.2
160 and over	8.1	11.1	6.0
Diastolic Blood Pressure (mmHg)			
Under 80	6.2	7.8	3.3
80-	7.8	7.3	3.3
90-	6.9	10.4	3.4
100-	7.2	12.5	(3.2)
110 and over	(15.4)	(12.3)	(3.8)
Weight (Kg)			
Under 70	7.6	6.1	3.8
70-	7.4	9.6	3.3
90 and over	7.1	10.0	(2.4)
Height (cm)			
Under 170	8.3	8.9	2.9
170-	6.7	9.4	3.0
180 and over	7.2	5.6	(5.9)
Quetelet Index ($\frac{W}{H^2}$ X 10,000)			
Under 26	8.0	8.4	3.7
26-	6.7	8.4	3.3
29 and over	7.7	11.0	(2.3)
Smoking			
Never smoked	4.2	5.8	(1.3)
Ex-smoker	4.4	5.5	(2.0)
Smoker	10.2	12.1	5.4
Amount Smoked (Cigarette smokers only)			
Under 10	11.4	(3.7)	(1.3)
10-	9.0	10.9	4.9
20 and over	10.1	14.9	6.3
Chest Pain			
Absent	6.8	8.5	3.7
Non-ischaemic	7.6	9.3	(2.1)
Positive questionnaire	(13.2)	(15.9)	(0.0)
Other pain	(13.2)	(9.3)	(6.8)
Leg Pain			
Absent	7.2	8.7	3.5
Non- ischaemic	7.4	9.2	(2.1)
Ischaemic	(22.4)	(19.1)	(0.0)
Arcus - Absent	7.0	8.5	3.3
Present	8.1	11.8	(3.5)
Xanthelasma - Absent	7.0	8.7	3.2
Present	(10.6)	(11.5)	(6.2)

(a) Median values were determined separately for the high cholesterol groups and low cholesterol group within each centre.

related to factors generally recognised as prognostically important in ischaemic heart disease. The rates shown are age-standardised and are surprisingly consistent with those expected from the results of other large population studies. In nearly every category, the incidence rises as the severity of the risk factor increases, and this applies to all 3 Groups, though at different levels. The exceptions are mostly associated with small numbers of events, but blood pressure as a risk factor deserves special mention. Compared with Group II, blood pressure in Group I had much less influence on the incidence of heart attacks.

MULTIVARIATE ANALYSIS

The data shown in Table 9, though striking in their regularity, take no account of the association of one factor with another and hence give no indication of the independent contribution of the various factors to prediction of outcome. For instance, the interesting relation between blood pressure and incidence of IHD might be due, partly or wholly, to a relation between blood pressure and age, smoking, or parental history. The appropriate statistical technique for taking account of these interrelations and producing a statement of the most important independent predictors of future IHD is some form of multivariate analysis. This has been carried out, using the multiple logistic function, as used, for instance, by Keys *et al.* (1972). Details of methods and results are given in Appendix 2.

In this analysis, carried out on men in Group II, in all centres, and excluding the clofibrate treated group for greater comparability with other published studies, the 5 variables which gave independently significant prediction of future IHD (fatal and non-fatal) were age, initial cholesterol, smoking, blood pressure, and whether the subject's father was alive at the start of the trial. Systolic blood pressure was a slightly more significant predictor than diastolic.

To give some idea of the magnitude of these effects (as distinct from their statistical significance) the following table shows the factors by which the risk of future IHD is increased for the indicated change in the variable concerned.

Variable	*Change*	*IHD risks multiplied by*
Age	+ 10 years	1·9
Smoking	present smoker of anything v. never or ex-smoker	2·4
Systolic blood pressure	+ 20 mmHg	1·3
Initial serum cholesterol	+ 20 mg/dl	1·2
Father dead at start of trial	dead v. alive	1·6

The 5 factors which, in the present analysis, give independently significant prediction are very similar to those shown in other prospective studies such as the Framingham Study, already mentioned, the 'Seven Country Study' (Keys *et al.*, 1972), or the study by Medalie *et al.* (1973) in Israel. The regression coefficients concerned are compared in Appendix 2. The coefficients for initial cholesterol are all very similar in these studies and, substituting the average reduction of 9% in cholesterol observed in this study in any of the equations results in a predicted reduction in the incidence of IHD of about 20 per cent, which was the reduction observed in the present study.

Directly to study the effects of treatment, on the other hand, the analysis was carried out on the men in Groups I and II, the treated and untreated high cholesterol groups.

The same 5 variables were included together with a sixth, treatment by clofibrate, that is membership of Group I or Group II. From this analysis treatment emerged as significant ($P < 0{\cdot}05$) and the effect was to reduce the incidence by 27 per cent. This figure is higher than the 20 per cent difference in incidence of major IHD reported above because of an accumulation of small differences in entry characteristics between the men in Groups I and II.

Cholesterol change, as previously defined, was next introduced as a variable (thereby automatically excluding all those who did not have a visit after the first, in whom, of course, no change could be measured). This was done, first, without including treatment and, secondly, including both treatment and cholesterol change. When cholesterol change but not treatment was included in the analysis, cholesterol change was significant and a reduction of 10 per cent in cholesterol (about 20 to 25 mg/100 ml) was associated with a reduction of 22 per cent in the risk. When both cholesterol change and treatment were included the significance of cholesterol change was slightly reduced but the effect of treatment was halved, suggesting that cholesterol change is associated with most (but not all) of the change in incidence resulting from treatment, that is that treatment may have some additional effect beyond that of cholesterol reduction. The excess effect is not itself significant.

OPTIMAL EFFECTS OF CLOFIBRATE ON MAJOR IHD EVENTS

Two approaches were used to find out whether there were any groups of subjects in whom clofibrate treatment was noticeably more, or less, effective than average in influencing major IHD events (fatal and non-fatal myocardial infarction).

The first, for which the results are set out in

TABLE 10

Differential Effect of Clofibrate

(a) By quartile of risk score

Major IHD events. Rates per 1000 per annum

Quartile of risk score	Group I Clofibrate		Group II High Cholesterol Control		Ratio of Rates (I/II)	Difference between Rates (II-I)
	No.	Rate	No.	Rate		
1 (lowest risk)	7	1.11	16	2.51	0.44	1.40
2	29	4.70	33	5.18	0.91	0.48
3	41	6.58	59	9.47	0.69	2.89
4 (highest risk)	78	12.56	93	16.28	0.77	3.72

Table 10(a), divided the men in the 2 high cholesterol Groups into quartiles of 'risk scores'. That is to say, a risk score was calculated for each man, based on the multiple logistic equation derived from Group II, and using the values of the 5 risk factors for that man at entry to the trial. This represented an assessment of his intrinsic risk of having a major IHD event. All the men in both Groups were ranked by this score and divided into 4 equal-sized quartiles of risk. For each such quartile, the number of major IHD events and the total number of man-years in the trial were determined to calculate a rate for each Group. The rates in the 2 Groups were then compared in each quartile. The difference varied from 0·48 per thousand per annum to 3·72, the highest differences being in the 2 quartiles of highest risk. The greatest proportionate change in the rates is in the lowest quartile of risk, whereas the greatest absolute difference in rates is in the highest quartile. From the point of view of achieving the greatest reduction in the number of cases of ischaemic heart disease, the difference is the more relevant index, and it suggests that the greatest benefit would derive from a policy of treating those at highest risk.

The second approach was to evaluate the effects of clofibrate treatment in subjects who had low and high values of the 5 main risk factors (age, smoking, cholesterol, systolic blood pressure, and father alive or dead). For each risk factor, the men in Group I were divided into those with low and high values and the number of events observed are shown in the first line of Table 10(b). In the second line, the 'calculated' number of events is shown. This calcu-

TABLE 10 (b)

Major IHD events in Group I by risk factors at entry to Trial

	Age		Smoking		Father		Systolic BP		Cholesterol		Greatest Effect	Remainder
	< 45	≥ 45	O+Ex	+	Alive	Dead	<135	≥135	≤median	>median		
Observed no. of events	30	125	43	112	14	141	77	78	58	97	45	110
Calculated no. of events	52	158	56	155	27	184	90	119	82	127	68	143
Observed rate/1000 p.a. (o)	2.88	8.63	3.80	8.24	2.25	7.55	5.58	7.02	4.68	7.76	9.46	5.46
Calculated rate/1000 p.a. (c)	5.02	10.93	4.91	11.42	4.36	9.84	6.55	10.71	6.60	10.13	14.30	7.10
R = ratio of rates (o/c)	0.57	0.79	0.77	0.72	0.52	0.77	0.85	0.66	0.71	0.77	0.66	0.77
D = difference between rates (c-o)	2.14	2.30	1.11	3.18	2.11	2.29	0.97	3.69	1.92	2.37	4.84	1.64

lated number, based on the multiple logistic function, is the number of events which would have occurred in the Group I men had they not been given clofibrate. The difference between observed and calculated numbers thus represents the effect of clofibrate treatment, making allowance for all the risk factors used in the logistic analysis. From the observed and calculated numbers, rates were derived and the ratios and differences of these rates are shown in the last two lines. Thus, for instance, in younger men aged under 45 years, the ratio of the rate in the clofibrate-treated group to the rate in similar men in Group II is 0·57 compared with 0·79 in the older men, suggesting a greater benefit of treatment in the younger men independently of other risk factors. On the other hand, the absolute differences due to treatment (2·14/2·30) do not differ appreciably between the younger and older groups. Similar contrasts between conclusions drawn from the ratio and the difference due to clofibrate treatment apply to parental history (ratios 0·52/0·77; differences 2·11/2·29) and to cholesterol (0·71/0·77; 1·92/2·37). For smoking, however, whether the ratios (0·77/0·72) or the difference (1·11/3·18) are taken as the best measure of the benefit of treatment, the result is similar, that is those at higher risk derive more benefit. This is even more so for systolic blood pressure (ratios 0·85/0·66; differences 0·97/3·69). These findings taken together with the results shown in Table 8, suggest that the men likely to benefit most from clofibrate treatment would be those with systolic blood pressure over 135 mmHg, who smoked, *and* who showed a reduction of cholesterol on treatment. This subgroup, comprising men of mean age 46·5 and mean cholesterol of 258 mg/100 ml, are described in Table 10(b) as those with 'greatest effect'. They are compared with the 'remainder', that is all other men in Group I. The ratios of major IHD rates in 'greatest effect' and 'remainder' subgroups were 0·66/0·77 and the differences 4·84/1·64. There is a 34 per cent reduction of events in the 'greatest effect' subgroup, compared with 23 per cent in the 'remainder'. These reductions in incidence are associated with mean cholesterol changes of 12 and 8 per cent, respectively. The 872 men in the 'greatest effect' subgroup represent 18·4 per cent of Group I, which in turn was selected from the upper third of the population. Thus this subgroup represents, at most, 6 per cent of men in the age range concerned.

TABLE 11

Serum Triglycerides (mg/dl)

Last in-trial reading for each man. Edinburgh only.

			Years in Trial		
			5	6	7
Group I	Clofibrate	Mean TG	161	158	162
		No. of men	178	294	592
Group II	High Cholesterol Control	Mean TG	205	211	209
		No. of men	184	276	601
Group III	Low Cholesterol Control	Mean TG	160	163	174
		No. of Men	181	248	658

CHANGE IN SERUM TRIGLYCERIDES DURING THE STUDY

As mentioned earlier under biochemical monitoring, serum triglycerides were measured in one centre only (Edinburgh) and then only from 1972. Since no baseline analysis was made, it is not possible to produce serial measures of individual change of triglyceride concentrations. Nevertheless, Table 11 shows that the concentrations after 5, 6, and 7 years of treatment with clofibrate were much lower than in the untreated high cholesterol group, and even slightly lower than in the low cholesterol control group.

Deaths from causes other than ischaemic heart disease

In the analysis of many conditions other than ischaemic heart disease there are good reasons for including deaths that occur after leaving the trial with those that occur in the trial. Deaths from cancer form an obvious example. The centres

TABLE 12

Deaths in the Trial and Within 1 year of Leaving it

Main Cause Groups. Numbers of Deaths & Rates at Ages 30-59, and Age-standardised Rates per 1000 per annum at ages 40-59

Cause of Death	Group I Clofibrate			Group II High Cholesterol Control			Group III Low Cholesterol Control		
	No. (All Ages)	Rate (All Ages)	St. Rate 40-59	No. (All Ages)	Rate (All Ages)	St. Rate 40-59	No. (All Ages)	Rate (All Ages)	St. Rate 40-59
Ischaemic Heart Disease	54	1.6	2.1	48	1.4	2.1	20	0.6	0.8
Other Vascular	14	0.4	0.5	14	0.4	0.6	9	0.3	0.5
Neoplasm: malignant	58	1.7	2.2	42	1.3	1.7	41	1.3	2.5
Neoplasm: benign	3	-	-	-	-	-	1	-	-
Other Medical Causes	16*	0.5*	0.8*	5*	0.2*	0.2*	7	0.2	0.4
Accidents and Violence	17	0.5	0.6	18	0.5	0.6	15	0.5	0.6
All causes other than IHD	108*	3.2*	4.1	79*	2.4*	3.1	73	2.3	3.9
All causes other than IHD, Vascular and Accidents & Violence	77**	2.3**	3.1*	47**	1.4**	1.9*	49	1.5	2.9
TOTAL ALL CAUSES	162*	4.9*	6.2	127*	3.8*	5.2	93	2.9	4.7

* Significant difference between Groups I and II ($P < 0.05$).

** " " " Groups I and II ($P < 0.01$).

differed, for valid local reasons, in their policies for excluding men from the study who developed malignant disease. On the other hand, it was not possible to be sure that all deaths occurring out of the trial were included. As mentioned earlier, a thorough search was made for all deaths occurring within one year of leaving the trial and, almost certainly, all but a few of these have been found. The figures in the report include all such deaths notified to the statistical centre up to the end of 1977. In this section, therefore, dealing with deaths from all causes, Table 12 shows the number of deaths and the unstandardised and age-standardised death rates for the principal causes of deaths occurring 'in the trial' and within 1 year of leaving it. Table 14 shows the numbers of deaths in more detailed categories of causes, and also distinguishes between deaths in the trial and those occurring within 1 year of leaving it. Such information as is available about deaths occurring out of the trial but *more* than 1 year after leaving it is available on request (Addendum E).

The total number of deaths was significantly greater in Group I (162) than in Group II (127, $P < 0{\cdot}05$), and the life-table analysis also shows a significant ($P < 0{\cdot}05$) excess in Group I. There was a slight excess of deaths from ischaemic heart disease in Group I but nearly all the difference between Groups I and II lies in the deaths from causes other than IHD. Here again the differences in total numbers (108 and 79) and in crude rates (3·2 and 2·4) are significant ($P < 0{\cdot}05$) and the life-table analysis gives a similar result ($P < 0{\cdot}05$, Fig. 5).

In terms of the individual cause groups other than IHD, shown in Table 12, the numbers of deaths from 'other vascular' conditions and from 'accidents and violence' are almost exactly the same in both groups, so that virtually the whole difference lies in deaths from cancer and from 'other medical causes', which are shown in detail in Table 14. However, when considering deaths from conditions not usually considered to be related to serum cholesterol level (which applies to the deaths in these 2 categories), it is appropriate to compare the mortality in Group I with that in Group III (the low cholesterol control group) as well as Group II, provided that in so doing allowance is made for the younger age at entry in Group III. (There are other differences between Group III and the other groups, but age is probably the most important. Appendix 2, multivariate table, Nos. 10, 11, and 12.) In Table 12 the age difference is taken into account by standardisation, and the effect of this adjustment is, of course, to increase the death rates in Group III compared with those in Groups I and II.

A comparison of the age-standardised rates in Groups I, II, and III for all causes other than IHD (4·1, 3·1, 3·9) suggests that part of the difference between Groups I and II is partly or largely the result of a low mortality in Group II rather than a high mortality in Group I. For cancer the corresponding rates are 2·2, 1·7 and 2·5 respectively, with a stronger indication of the same point.

Because of its importance, a detailed follow-up of all in- and ex-trial morbidity and mortality due to cancer was carried out. Table 13 shows that there was little difference between Groups I and II (66 cases against 61) in ex-trial deaths and cases still surviving. The main difference between these Groups thus lies in the in-trial mortality. Comparing all 3 Groups, the standardised rates for all malignant neoplasms are 3·6, 2·8, and 3·4, and for mortality,

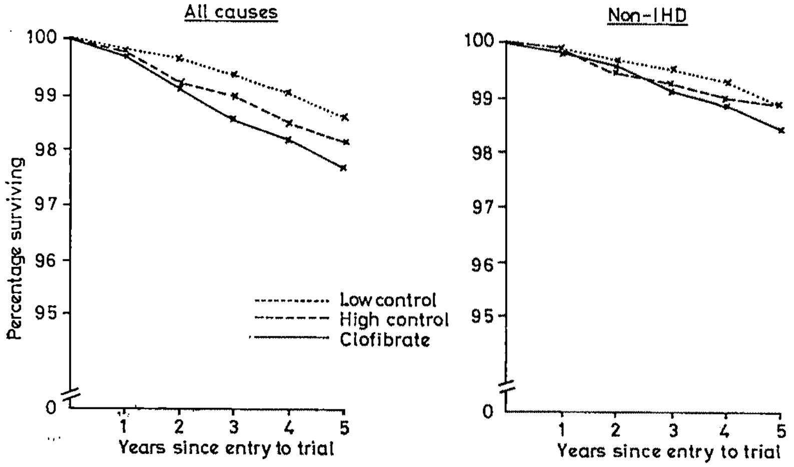

Fig. 5 *Total mortality. In-trial and within 1 year of leaving. Life-table basis.*

TABLE 13

Malignant Neoplasms

	Group I	Group II	Group III
	Clofibrate	High Cholesterol Control	Low Cholesterol Control
Deaths:			
In-trial	40	24	30
Ex-trial: within 1 year	18	18	11
after 1 year	20	13	11
Still living at 31.12.76	28	30	24
Total known cases	106	85	76
Standardised Rate (all malignant neoplasms) 40-59 per 1000 per annum	3.6	2.8	3.4
Standardised Death Rate 40-59 per 1000 per annum (in-trial & within 1 year)	2.2	1.7	2.5

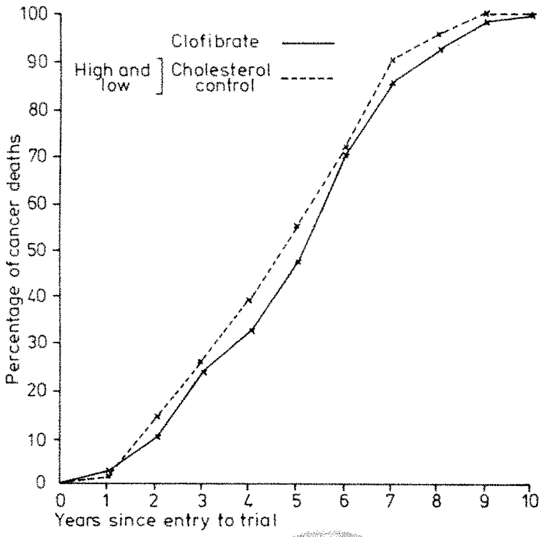

Fig. 6 *Cumulative cancer mortality by years in trial. Total cancer deaths in and out of trial.*

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2·2, 1·7, and 2·5, respectively. Fig. 6 compares the cumulative percentage of cancer deaths occurring in Group I with those occurring in Groups II and III at different times after entry. The curves are almost identical.

The remaining deaths which show a difference between Groups I and II are those resulting from 'other medical causes', and again the difference is confined almost entirely to the in-trial deaths (16 and 5, overall, 15 and 3 in-trial). Though the numbers are much smaller, these differences are significant. There is, however, once again, the suggestion, when age-standardised rates for all deaths in the trial and within one year of leaving it in all three groups are compared (0·8, 0·2, and 0·4) that Group II may have a fortuitously low rate. Deaths from disease of the liver and gall bladder appear among the detailed causes of the excess in this group, and there is an excess in Group I of deaths from cancer of these sites and of the intestines. These issues are taken up in the discussion and Table 17.

Because of the suggestion in the report of the

TABLE 14

Deaths in the Trial and Within 1 year of Leaving it[(a)]

Detailed Causes, distinguishing deaths in the Trial from those out of the Trial

Numbers of deaths at ages 30-59

Cause of Death	Group I Clofibrate			Group II High Cholesterol Control			Group III Low Cholesterol Control		
	In-Trial	Out of Trial within 1 year	Total	In-Trial	Out of Trial within 1 year	Total	In-rial	Out of Trial within 1 year	Total
Ischaemic Heart Disease									
Within 3 hours	23	9	32	17	8	25	8	2	10
More than 3 hours	13	9	22	17	6	23	8	2	10
Total	36	18	54	34	14	48	16	4	20
Other diseases of the Circulatory System									
Cerebrovascular disease	8	1	9	7	3	10	3	2	5
Thrombophlebitis	4	-	4	3	1	4	-	-	-
Chronic pulmonary heart disease	1	-	1	-	-	-	1	2	3
Other diseases of circulatory system	-	-	-	-	-	-	-	1	1
Total	13	1	14	10	4	14	4	5	9
Malignant Neoplasms									
Oesophagus, stomach	6	3	9	4	1	5	6	2	8
Small intestine, colon, rectum	6	5	11	3	3	6	3	2	5
Liver, gall bladder, pancreas	6	1	7	3	2	5	5	-	5
Larynx, bronchus and lung	13	4	17	7	4	11	10	4	14
Skin	2	-	2	2	-	2	2	1	3
Brain	4	1	5	2	3	5	1	1	2
Haematopoietic tissue	2	-	2	1	2	3	1	-	1
Other, or not known	1	4	5	2	3	5	2	1	3
Total	40	18	58	24	18	42	30	11	41
Benign Neoplasms	3	-	3	-	-	-	1	-	1
Other Medical Causes									
Pulmonary Tuberculosis	1	-	1	1	-	1	-	-	-
Diseases of the Central Nervous System	-	-	-	-	1	1	-	-	-
Diseases of the Respiratory System									
Influenza	1	-	1	-	-	-	-	-	-
Bronchopneumonia	1	-	1	-	-	-	2	-	2
Chronic Bronchitis	1	-	1	1	-	1	-	-	-
Peptic Ulcer	2	-	2	1	-	1	2	-	2
Liver & Gall Bladder Diseases									
Acute Hepatitis	1	-	1	-	-	-	-	-	-
Liver cirrhosis	-	-	-	-	-	-	1	-	1
Cholecystectomy (see Table 16)	3	-	3	-	-	-	1	-	1
Pancreatitis	2	1	3	-	-	-	-	-	-
Diseases of the Genito-urinary System									
Chronic pyelonephritis	1	-	1	-	-	-	-	-	-
Calculus of kidney	1	-	1	-	-	-	-	-	-
Hyperplasia of Prostate	1	-	1	-	-	-	1	-	1
Chronic Osteomyelitis	-	-	-	-	1	1	-	-	-
Total	15	1	16*	3	2	5*	7	-	7
Accidents & Violence									
Injuries, homicide, accidents	13	-	13	13	1	14	11	1	12
Suicide	4	-	4	2	2	4	3	-	3
Total	17	-	17	15	3	18	14	1	15
TOTAL all Causes other than IHD	88	20	108*	52	27	79*	56	17	73
TOTAL ALL CAUSES	124	38	162*	86	41	127*	72	21	93

(a) Deaths occurring more than one year after leaving the Trial, so far as they are known, are shown in Addendum E.

* Significant difference between Groups I and II ($P < 0.05$).

TABLE 15

Withdrawals for Medical Reasons other than Major Ischaemic Heart Disease

Reason for Withdrawal	I.C.D. No.	Group I Clofibrate	Group II High Cholesterol Control	Group III Low Cholesterol Control
Minor IHD		10	9	5
Other Vascular Events (See Table 5)		128	139	90
Infective & Parasitic Diseases	000-136			
Pulmonary tuberculosis	011	3	5	6
Viral hepatitis	070	9	9	11
Other		2	-	1
Neoplasms (malignant & benign)	140-239	13	12	9
Endocrine & Metabolic Diseases	240-279			
Diabetes (See Table 5)	250	47*	26*	18
Weight gain	277	9*	2*	2
Other		5	9	5
Mental Disorders	290-315			
Psychoses	290-299	2	-	2
Neuroses & other non-psychotic disorders	300-309			
Impotence	305.6	14	7	6
Other		1	2	4
Diseases of the Nervous System	320-389	4	7	4
Diseases of the Respiratory System	460-519	1	-	1
Diseases of the Digestive System	520-577			
Peptic Ulcer	533	5	11	6
Indigestion, nausea, etc.	536.9	20	30	37
Diarrhoea, etc.	561	9	8	11
Other, including diseases of liver and gall bladder		24	19	22
Diseases of the Genito-urinary System	580-629	3	2	4
Diseases of the Skin	680-709			
Hair loss	704	-	1	-
Other		1	3	2
Diseases of the Musculo-skeletal System	710-738	1	2	-
Symptoms & Ill-defined conditions	780-796			
Dizziness	780.5	4	1	1
Pains in the joints & muscles	787	1	2	1
Rash	788.2	7	13	10
Fatigue	790.1	7	2	3
Other		15	5	10
Accidents	800-999	1	1	1
TOTAL		346	327	272

* Significant difference between Groups I and II ($P < 0.05$).

TABLE 16

Cholecystectomies for Gallstones

	Group I	Group II	Group III
	Clofibrate	High Cholesterol Control	Low Cholesterol Control
(i) Numbers and Rates			
No. of men admitted to trial:-	5331	5296	5118
No. of cholecystectomies for gallstones in:-			
Edinburgh	22	4	10
Budapest	18	11	9
Prague	19	9	6
All Centres: No.(a)	59***	24***	25
Rate	2.1***	0.9***	0.9
Age-stand. rate (b)	2.0	1.2	1.6
(ii) Numbers in relation to Time in Trial			
Years in Trial: <2	11	2	5
2-	17	7	6
4-	18	11	10
6 & over	12	4	4
Not known	1	-	-
Total	59	24	25

(a) Includes 4 deaths (see Table 14).

(b) Age-standardized 40-59.

*** Significant difference between Groups I and II ($P < 0.001$).

American Coronary Drug Project Research Group (1975) that clofibrate may have led to thromboembolic complications, a special examination of the death-record forms in the present study was carried out, under 'blind' conditions, to study whether deaths occurring after surgery, for example, might have been more commonly associated with thrombotic or embolic phenomena in Group I. The numbers for Groups I and II were not significantly different (6 *v* 3).

The differences in total mortality between Groups I and II were most obvious in Budapest and least in Edinburgh (Appendix 4) and this was most noticeable in death from causes other than IHD. As with deaths in the trial as a whole, however, the age-standardised mortality in Group III exceeded that in Group II.

WITHDRAWALS FOR MEDICAL REASONS

Table 15 shows the variety of conditions, some of

TABLE 17

Regional Pathology

Numbers of deaths in the trial and within 1 year of leaving it, at ages 30-59

Site of Pathology	Deaths from "Other Medical Causes"(a)			Deaths from Malignant Neoplasms			All Deaths at these sites		
	I	II	III	I	II	III	I	II	III
Liver	1	0	1	3	1	1	4	1	2
Gall bladder	3	0	1	1	0	0	4	0	1
Small intestine	0	0	0	1	0	0	1	0	0
Colon	0	0	0	6	5	3	6	5	3
Rectum	0	0	0	4	1	2	4	1	2
Total	4	0	2	15	7	6	19*	7*	8
Rates per 1000 per annum	-	-	-	-	-	-	0.57*	0.21*	0.25
Age-standardised rates (40-59)	-	-	-	-	-	-	0.75**	0.17**	0.65

(a) See Table 14.

* $P < 0.05$

** $P < 0.01$

which were suspected of being adverse reactions, which caused withdrawal from the trial. Cholelithiasis was not known as an adverse effect of clofibrate until half-way through the trial and was not listed as such. A preliminary report on the incidence of cholecystectomy for gall stones occurring in the trial has already been published (Cooper *et al.*, 1975). Table 16 (i) shows the final position, confirming beyond doubt the previous reports. Four of these men died in the perioperative period from sepsis or other complications, 3 in Group I and 1 in Group III.

'Indigestion', 'diarrhoea', and 'skin reactions' were specifically recorded at follow-up visits because they are well recognised side-effects of clofibrate. Table 15 shows that none of these three caused withdrawal from the trial more frequently from Group I than from the other groups. Weight gain, hair loss, muscle cramps, and cardiac arrhythmia are also listed because they have been questioned as possible adverse effects of clofibrate. Only weight gain accounts for a significant difference ($P < 0{\cdot}05$) between Groups I and II, but the numbers are very small (9 *v* 2).

The category 'other' includes a variety of complaints such as thirst, insomnia, vertigo, headache, and intolerance to alcohol. The numbers were too small to allow for statistical appraisal of individual conditions.

The centres differed considerably in the number of subjects withdrawn for medical reasons (Addendum C). Numbers were greater in Prague than in either of the other two centres; the conditions where this excess was most noticeable were diabetes, hypertension, 'other digestive' conditions, and infective hepatitis.

CONDITIONS NOT NECESSARILY CAUSING WITHDRAWAL FROM THE TRIAL

Such conditions, recorded as possible side-effects of treatment, are shown in Appendix 6.

Approximately 13 per cent of men reported one of the conditions listed on at least one occasion (distribution between Groups was 15, 12, and 12 per cent ($P < 0{\cdot}01$)). Specific conditions are mentioned in the discussion. There were, however, substantial intercentre differences.

Various bizarre effects were attributed to the trial capsules, there being no significant difference in incidence between groups. Interestingly, increased sweating was reported as being more common in Group I than in Group II, but only at Edinburgh, where the difference in incidence was statistically significant (24 *v* 7, $P < 0{\cdot}01$). No cases had to be withdrawn from the trial because of this symptom.

Discussion

PRINCIPAL FINDINGS

The trial has shown that healthy men, aged 30 to 59, with moderately raised serum cholesterol levels who were treated with the cholesterol-lowering drug clofibrate had significantly fewer major IHD events than comparable controls ($P < 0{\cdot}05$). This reduction was confined to non-fatal myocardial infarcts ($P < 0{\cdot}05$). The incidence of fatal first IHD events, whether within or after 3 hours of onset of symptoms, did not differ significantly in the two groups. There were in the trial and within 1 year of leaving it significantly more deaths from all causes in those treated with clofibrate compared with the control groups (162, 127, and 93). This excess occurred mainly in the deaths from causes which were not due to IHD, other vascular disease, or accidents (77, 47, and 49 deaths).

Reviewing the assumptions made in planning this trial, the actual fall in serum cholesterol was less than the initial forecast of 15 per cent; the incidence of IHD at ages 30 to 59 in the high cholesterol control group was 0·74 per cent compared with a predicted 1 per cent; the reduction in incidence of IHD achieved in the treated group was 20 per cent compared with 30 per cent on which the original calculations were based. This was significant at the 5 and not the 1 per cent level. The total number of men recruited, however, was 15 745 compared with 15 000 and the number of man-years experienced 83 534 against the postulated 75 000. The period of study was, of course, not 5 years for each individual though the average length of time in the study was 5·3 years: some were in the trial for 8 years and a few for only 4. The actual percentage of men lost to the trial for all reasons in the first 5 years was 31 per cent compared with the assumed 30 per cent.

ISCHAEMIC HEART DISEASE

(a) Mortality

The failure of clofibrate to reduce the incidence of fatal heart attacks is disappointing. The prevention of non-fatal infarction, however, might be expected to result in improved long-term mortality, since men with a history of myocardial infarction have a worse prognosis than those without such a history. Mortality from IHD, particularly early death, was not reduced in other primary prevention trials using a diet rich in polyunsaturated fats (Dayton *et al.*, 1969; Miettinen *et al.*, 1972); and the Albany-Framingham study has shown that the incidence of sudden death bears no relation to prior serum cholesterol levels (Kannel *et al.*, 1975). The mechanisms responsible for such deaths are probably less directly related to serum cholesterol change and the amount of coronary atheroma than those leading to non-fatal myocardial infarction. Deaths within 3 hours of the onset of symptoms are mostly the result of primary ventricular arrhythmias, probably resulting from acute myocardial ischaemia. Deaths more than 3 hours and less than 28 days after onset of symptoms are mostly related to the extent of the infarct itself and are the result of secondary arrhythmias, cardiogenic shock, heart failure, and rupture of the ventricle.

(b) Non-fatal myocardial infarcts

The results reported relate only to events occurring during the trial, when the men were taking the capsules. No systematic attempt was made to ascertain non-fatal myocardial infarcts after the end of treatment. Available data were examined, however, to identify any 'rebound' effect after withdrawal of clofibrate and there was no difference between Groups I and II in the incidence of total IHD after 3 months, 6 months, or 1 year.

Most of the difference in incidence of non-fatal myocardial infarction between Groups I and II appears to be related to cholesterol reduction. The effect of reducing cholesterol with clofibrate was to lower the incidence whatever the initial concentration and this is well illustrated by comparing Groups I and II in Table 8. Men with high initial serum cholesterol concentrations had a worse prognosis in both Groups, whatever changes occurred during the trial period. The highest incidence rates for all IHD in the high cholesterol control group occurred in those with initial concentrations above the median, that is in the upper sixth of the total cholesterol distribution for the populations studied. Cholesterol 'non-responders' comprised a substantial minority (about a sixth) of Group I, and the higher incidence rates of IHD events in these partly dilutes the results for the Group as a whole. Under conditions of ordinary medical practice such patients would be considered as 'failures', and an unsatisfactory regimen would be replaced with a potentially better one.

The extent to which concurrent reduction of elevated serum triglycerides could have contributed to the reduction in non-fatal IHD cannot be assessed from our data.

(*c*) *Optimal effects of clofibrate on major IHD events*

An attempt was made to identify those most likely to benefit from clofibrate treatment. In this trial, they were men who had a reduction of serum cholesterol on treatment and had a systolic blood pressure of over 135 mmHg and who smoked. This subgroup, comprising men with a mean age of 46·5 years and a mean initial serum cholesterol of 258 mg/100 ml had a 34 per cent reduction in major IHD events compared with a 23 per cent reduction in the remainder in Group I. These reductions in incidence were associated with mean serum cholesterol changes of 12 per cent and 8 per cent, respectively. This subgroup represents, at most, 6 per cent of the men in the age range concerned.

(*d*) *Angina and myocardial ischaemia*

The incidences of angina pectoris occurring during the trial, whether with or without supporting electrocardiographic evidence, and of electrocardiographic signs of myocardial ischaemia in the absence of chest pain, were similar in Groups I and II. A decreased rate of development of the earliest symptoms of IHD might have been expected if clofibrate slowed the pace of narrowing in the coronary arteries. This was suggested in the results of the Scottish and Newcastle trials of clofibrate in patients with angina (Dewar and Oliver, 1971). But neither was specifically designed to test the possibility and a new trial was proposed. Results of the current study do not help to answer this question.

MORTALITY FROM ALL CAUSES

There were 162 deaths in the clofibrate-treated group during and in the first year after the trial compared with 127 in the high cholesterol control group and 93 in Group III (Table 12). The excess of 35 deaths between Groups I and II is significant ($P < 0{\cdot}05$); 6 of the 35 were due to IHD and 29 to causes not usually associated with serum cholesterol concentrations or changes. The difference in overall crude rates was also significant ($P < 0{\cdot}05$). The design of the trial provided a second control group (Group III) which, though chosen on the basis of relatively low initial cholesterol levels, should also be used for such comparison provided that correction is made for the fact that men in this group were slightly younger than those in Groups I and II. Age-standardised rates have been used for comparison for this purpose, since the multiple logistic analysis shows that correcting for other factors as well as age adds very little. There was no significant difference in age-standardised mortality from all causes between any of the Groups.

Numbers of deaths due to other vascular causes and from accidents and violence were similar in Groups I and II. The greater part of the excess in Group I was distributed over a wide range of medical conditions classified in Table 12 under 'malignant neoplasms' and 'other medical causes' and detailed further in Table 14. These two main categories, taken together, show an excess in Group I over Group II (77 *v* 47; $P < 0{\cdot}01$), and the crude rates were also significantly in excess ($P < 0{\cdot}01$). Though there was a significant difference in age-standardised rates (3·1 and 1·9; $P < 0{\cdot}05$) between Groups I and II, there was virtually none between Groups I and III (3·1 and 2·9), suggesting that the rates in Group II may be spuriously low.

(*a*) *Malignant neoplasms*

The excess in Group I over Group II of deaths due to cancer occurred mostly during the trial (40 *v* 24), and not in ex-trial deaths either within or after 1 year (38 *v* 31) or in those with diagnosed cancer still alive at the end of the trial (28 *v* 30). While neither the numbers nor the crude rates are significantly in excess, this might suggest that, while not being carcinogenic, clofibrate could have accelerated pre-existing cancer and have led to earlier death. But the cumulative percentages of cancer deaths occurring in Group I compared with Group II at different times after entry are almost identical (Fig. 6) and what difference there is suggests a later, rather than an earlier, mortality due to cancer in Group I. The age-standardised death rates in the three groups were 2·2, 1·7, and 2·5. The corresponding age-standardised rates for deaths from malignant neoplasms calculated from the official mortality statistics for men of the same age in the Edinburgh area, Budapest, and Prague are as follows: 2·2 (East Central and South Scotland, 1969-73), 2·6 Budapest (1972-74), 2·8 Prague (1968-73). These figures are surprisingly close to the rates observed in trial subjects in Groups I and III.

Thus the data for all cancer do not give rise to special concern.

(*b*) *'Other medical causes'*

There was a significant excess in deaths and crude death rates from 'other medical causes' in the clofibrate-treated group compared with the high cholesterol control group (16 and 5; 0·5 and 0·2; $P < 0.05$). This excess was most evident in Budapest and virtually absent in Edinburgh (Appendix 4). The age-standardised death rate in the clofibrate-treated group was significantly higher than in the high cholesterol control group but not significantly greater than in the low cholesterol control group.

Though the numbers are small, these results have caused much concern and particular care has been given to accurate assessment of necropsy reports, which were interpreted without knowledge of treatment groups by 2 observers. Of the 28 patients dying from 'other medical causes', 25 had necropsies performed.

Regional pathology

There were more deaths from diseases of the liver, gall bladder, and intestines, including malignant neoplasms of these sites, in the clofibrate-treated group than in the high cholesterol control group. Taken together with the significant excess in the treated group compared with both control groups of cholecystectomies for gall stones, there was therefore a possibility that clofibrate might be producing pathology in this area. The relevant mortality data are collected in Table 17. The difference in numbers of deaths between Groups I and II (19 *v* 7) is significant ($P < 0.05$) as also is the difference between age-standardised rates ($P < 0.01$). On the other hand, the similarity of the age-standardised rates in Groups I and III gives some reassurance, suggesting that the low rate in Group II may have been fortuitous. The numbers concerned are small. This shows up in the contrast between the crude and age-standardised rates for Group III. The proportions of all deaths not due to IHD but due to pathology of the liver, gall bladder, and intestines were 19/108 = 18 per cent in Group I, 7/79 = 9 per cent in Group II, and 8/73 = 11 per cent in Group III. On entry, men who subsequently died from the causes shown in Table 17 were, on average, a few years older, slightly heavier, and more likely to have fathers who have died than the rest of the men in the same treatment group.

Although the statistical impropriety of retrospectively selecting a particular subgroup for analysis is fully recognised, investigators have to draw attention to any unexpected biological finding which might relate to the conclusions as a whole. A plausible biological hypothesis can be stated in support of the subgrouping shown in Table 17, and no other subgrouping of data or of major endpoints (other than IHD) has shown significant differences between the clofibrate-treated and high cholesterol control groups. The hypothesis is that clofibrate, through mobilisation of cholesterol from tissue pools (including arteries) resulting in excretion of cholesterol and related sterols, could contribute to liver, biliary, and intestinal pathology.

The mechanisms through which clofibrate might do this are not understood. It has been shown that after 3 years of daily administration of the drug, there is continued increase in excretion of cholesterol into the bile. There is also *enhanced* excretion of endogenous neutral sterols and this exceeds a *decrease* in acid sterol excretion (Grundy *et al.*, 1972). No study has been reported of the relation of increased neutral sterol excretion to large bowel pathology, though *raised* faecal acid sterol concentrations have been implicated in the pathogenesis of cancer of the colon (Hill *et al.*, 1975). Other possibilities are that clofibrate has some effect in altering intestinal bacterial flora; or that directly or indirectly it causes aromatisation of certain bile acids (Hill, 1977), leading to tissue damage. Another potent hypolipidaemic drug, nicotinic acid, also increases neutral sterol excretion (Einarsson *et al.*, 1977).

In the Los Angeles Veterans Administration Study (Dayton *et al.*, 1969), there were more deaths from non-atherosclerotic causes in the group receiving a polyunsaturated fat diet than in an untreated control group. In particular, there were more deaths caused by malignant disease in the treated compared with the control group (31 *v* 17), but further analysis of the results of this and other dietary studies disclosed no significant excess incidence of cancer in the experimental groups (Ederer *et al.*, 1971). S. Dayton (1978, personal communication) has recently reanalysed his data and there was no evidence of excess pathology, including cancer, specifically in the liver, biliary, and intestinal systems in the diet group compared with controls. In the Helsinki Mental Hospital Study of the primary prevention of IHD (Miettinen *et al.*, 1972) there was also a non-significant excess in total mortality among the experimental group taking a polyunsaturated fat diet. Age-adjusted death rates/1000 person-years for malignant neoplasms (5·02 diet *v* 3·96 control) and 'other diseases' (15·45 diet *v* 13·03 control) were both greater in men receiving the cholesterol-lowering diet. No data are available concerning regional pathology.

MORBIDITY

Cholecystectomies

The figures for cholecystectomy operations for gall stones shown in Table 16 confirm our own (Cooper *et al.*, 1975) and other (Coronary Drug Project, 1975) reports that gall stone formation is an adverse effect of clofibrate therapy. Interestingly, the difference in incidence of cholecystectomy between Groups I and II appears to be greater, though not significantly, in the first 4 years of clofibrate treatment than later and does not increase with time. (Table 16 (ii)).

No attempt was made in the trial to determine the prevalence of gall stones, but clofibrate is known to decrease bile solubility leading to greater lithogenicity (Pertsemlidis *et al.*, 1974). Diets with a high polyunsaturated/saturated fat ratio have also been reported to increase the incidence of gall stones (Sturdevant *et al.*, 1973). Nicotinic acid also increases cholesterol saturation of bile and may increase the risk of gall stone formation (Leijd *et al.*, 1978). Perhaps any procedure that promotes cholesterol excretion can lead to gall stone formation.

Hypertension

There were significantly fewer notifications ($P < 0{\cdot}05$) and withdrawals ($P < 0{\cdot}01$) because of hypertension in Group I compared with Group II (Table 5). The explanation of this is not clear, though clofibrate may have prevented the development of hypertension in some patients. Support for this suggestion comes from the relatively weak relation in Group I between systolic or diastolic blood pressure at entry to the trial and the incidence of IHD. This might be expected if the beneficial effects of clofibrate were stronger than the adverse effects of developing hypertension as shown by the expected relation between blood pressure and prognosis in Group II. However, clofibrate did not appreciably lower blood pressure in Group I as a whole.

Intermittent claudication

There was no significant difference in the reported incidence of intermittent claudication. A clinical study, conducted without knowledge of treatment groups, confirmed that there was no difference between the groups in signs of peripheral arterial disease.

Cardiac arrhythmias

The incidence of cardiac arrhythmias was not significantly different in Groups I and II. Electrocardiograms, however, were recorded only from the time taken to complete a 12-lead record and not for longer periods for rhythm detection.

Cerebrovascular events

There was no significant difference in fatal or non-fatal cerebrovascular events between Groups I and II. The combined figures for the 3 Groups were 27, 23, 19.

Thromboembolic events

The slight excess in Group I compared with Group II of cases of non-fatal thromboembolism causing withdrawal from the trial (7 *v* 2) was not reflected in an excess in fatal thromboembolism (4 and 4).

Diabetes mellitus

The apparent excess in Group I compared with Group II in 'diabetes mellitus requiring drug treatment' requires comment. Glucuronic acid, which can result from clofibrate glucuronide, can cause false positive urine tests but would not affect glucose tolerance tests. A special investigation during the terminal stages of the trial was carried out in Prague, which accounted for more than half of the cases. All men showing glycosuria in Prague had been referred to a department of diabetes for glucose tolerance tests and a decision regarding treatment, and possibly this accounted for part of the higher number of cases there. On final review a few cases were not confirmed. However, withdrawals at Budapest were also more numerous in Group I than Group II, though not significantly so.

These findings are puzzling in view of the number of published reports indicating that clofibrate has a beneficial effect on glucose tolerance and probably on insulin sensitivity (Barnett *et al.*, 1977; Enger *et al.*, 1977; Lithell *et al.*, 1977). The latter two studies involved men with clinically latent diabetes discovered during a health screening programme and are, therefore, perhaps comparable with our own. The long-term effects of clofibrate treatment on diabetes in 50 hyperlipidaemic patients followed for 6 to 8 years were favourable (Berkowitz, 1971).

Withdrwals and reported side effects

Significantly more of the few men who were withdrawn from the trial for weight gain were in Group I than in Group II (Table 15), and significantly more men in Group I reported weight gain (Appendix 6). In fact, however, differences between mean weights during the trial for all men in the 2 groups were trivial. Impotence was also reported significantly more often by men in Group I than in Group II but no attempt has been made to establish its real incidence. Diabetes has been discussed above. Gastrointestinal symptoms and diarrhoea were also reported significantly more commonly in Group I but were transient or quickly reversed on stopping medication.

TRIGLYCERIDES AND LIPOPROTEINS

The absence of analyses of serum triglycerides or of lipoprotein fractions at the start of the trial requires comment. This trial was initiated in the 3 centres between 1965 and 1968 and methods for serum triglyceride and lipoprotein analysis were still being developed at that time; automated systems for estimation of plasma lipids were not available to the centres at the start of the trial. The clinical importance of specific lipoprotein types was first described after the start of the trial (Frederickson *et al.*, 1967) and internationally standardised by the World Health Organisation only in 1970. It is one of the fallibilities of long-term trials that methodology can improve to such an extent that the original design appears inadequate.

As mentioned earlier, serum triglycerides were measured in one centre only and the results confirm the well-known observation that clofibrate reduces serum triglycerides even more than serum cholesterol. It is particularly interesting that the concentrations in the treated group approximate to those in the low cholesterol control group. In view of the suggested importance of raised serum triglycerides as a risk factor for IHD (Brown *et al.*, 1965; Carlson and Böttiger, 1972), their obvious reduction by clofibrate may also have contributed to the reduction of non-fatal IHD events.

CHARACTERISTICS OF CONTROL GROUPS

A low and a high cholesterol control group were included in the trial to provide additional means of appraising the response of the treatment group. For example, the importance to the community of changes in IHD incidence would be enhanced if the difference between treated and control high-risk groups was such that the incidence in the treated group approximated that of a low-risk control group. The inclusion of putatively high and low risk control groups also provides actual evidence for the community under study that the groups chosen do have a spectrum of risk.

The incidence of IHD in the high cholesterol control group was less than predicted. A degree of 'placebo response' is to be expected but this might not affect high and low risk groups equally. Attention to their health by attendance at clinics, blood tests, and the daily swallowing of capsules is likely to lead to 'correction' of more adverse habits in the group with the most adverse habits. Thus, the high cholesterol control group might be likely to alter the diet, stop their higher cigarette smoking, and increase physical activity more than the low cholesterol control group. Such changes could militate against being able to show highly significant differences compared with a treated high-risk group. Though we suspect that the rates in Group II for some major end-points not related to IHD and vascular events may be unrepresentatively low, this cannot be proved because the actual rates for these end-points are not known specifically for high cholesterol populations.

The men in Group III—as well as having lower serum cholesterol levels—were younger, lighter in weight, had lower blood pressure, and smoked less. As expected, their risk of IHD was relatively low. To some extent, the mortality figures for IHD for this group are reassuring when assessing the meaning of the differences between Groups I and II, and the age-standardised rates for deaths from causes other than IHD are more closely related in all categories to those for Group I rather than Group II.

CONDUCT OF THE TRIAL

From an early phase of the study, there was an unfavourable trend in mortality from all causes. By the end of 1972, this came near to the 10 per cent significance level on a sequential basis and the principal investigators were informed. During 1973, the figures improved somewhat, but by the end of 1974 the unfavourable trend in overall mortality was resumed though still not reaching the 10 per cent level. Because of this, and the fact that an interim assessment suggested that there were disappointing benefits in terms of the main objectives of the study—reduction of the incidence of all IHD events—the possibility was seriously considered in 1975 that the trial should be terminated prematurely and the findings reported.

It was agreed, however, that an intensive study should first be made into the deaths from cancer, as there was a suggestion at that time of an excess in the mortality figures in Group I. This involved a major investigation into available information on morbidity as well as mortality of men in the trial, and men who had left the trial, including reviews of all relevant clinical and necropsy records, searches of national and local cancer registers, and reappraisal of all the death certificate data. The results of this inquiry reported in Tables 12 and 13 and Fig. 6 are reassuring.

The investigators were agreed that premature closure of the trial and release of results was inadvisable until the special study of cancer was complete. Meanwhile, the adverse overall trend of mortality in Group I had continued and it neared the 5 per cent significance level late in 1976. By this time, the trial was already being closed and this process was accelerated.

These developments presented the investigators with difficult and anxious decisions and they emphasise that it is mandatory in such long-term trials to apply rigorous monitoring of all supposedly therapeutic regimens.

OTHER PRIMARY PREVENTION TRIALS

The results of our study are in some accord with those of the only other published trial of the primary prevention of ischaemic heart disease using clofibrate. But this was an incompletely randomised study, not conducted 'blind', and the first report (Krasno and Kidera, 1972) has been severely criticised (Feinstein, 1972). The greater reduction in incidence of non-fatal myocardial infarction was associated with a reduction in serum cholesterol of 40 mg/100 ml (L. R. Krasno, 1978, personal communication). This was achieved by a high degree of rapport between the physicians and the subjects, who were fully aware of their individual cholesterol levels.

The results of the only other large long-term primary prevention trial (Miettinen *et al.*, 1972) are relevant to the findings of the present trial. Mean serum cholesterol reduction in middle-aged men and women in two mental hospitals, given a diet with polyunsaturated/saturated (P/S) ratio of 1·42 to 1·73 on a cross-over design, ranged from 12 to 18 per cent compared with the control periods when they received a normal hospital diet. When the results for the treated groups were pooled, there was a significant reduction in IHD mortality ($P < 0{\cdot}02$): no data are available concerning morbidity. There are, however, weaknesses in the design and conduct of the Helsinki Mental Hospital Study and the authors refer carefully to some of these. Others have been emphasised by Halperin *et al.* (1973), who concluded that the data 'may not be of sufficient strength . . . to establish the diet hypothesis and to draw the authors' conclusions'.

Another relevant carefully controlled long-term prevention trial is the Los Angeles Veterans Administration Study (Dayton *et al.*, 1969). This used a double-blind design but was not exclusively a primary prevention study and included, as a minority, patients with pre-existing complications of atherosclerosis. It was conducted in an elderly male population and the effects of a diet high in polyunsaturated fats and low in saturated fats were compared with a control diet comprising fat calories mostly of animal origin. The difference in serum cholesterol between the treated and control groups was 12·7 per cent. There was no difference in the incidence of fatal events, whether sudden or not, but there was a 31 per cent decrease in non-fatal myocardial infarction. This was not statistically significant, but pooling of the data in all subjects (primary and secondary prevention) for all other vascular events, particularly cerebral infarction, showed significant reduction in the 8-year incidence rates in the diet group ($P = 0{\cdot}01$). There were 85/424 deaths resulting from non-atherosclerotic causes in the diet group and 71/422 in the control group.

SECONDARY PREVENTION TRIALS USING CLOFIBRATE

The results in terms of IHD of secondary prevention diet and drug trials are not directly relevant to those of this trial and to the primary prevention trials briefly described above, because the natural history of the development of IHD has probably already been determined by the occurrence of myocardial infarction and because of the inevitable selection of the populations studied. But brief mention is made of non-cardiovascular deaths in the only two which used clofibrate.

In the Coronary Drug Project (1975), the percentages (based on 5-year rates) who died from a non-cardiovascular event was 2·1 in the clofibrate-treated group, 2·1 in the nicotinic acid-treated group, and 1·5 in the placebo group. Cancer deaths were equally distributed, giving a slight excess of non-cardiovascular and non-cancer deaths in the treated groups (1·5% and 1·5%) over the placebo group (0·9%); the slight and non-significant excess in the clofibrate group only became evident during the seventh year of treatment.

The secondary prevention trials using clofibrate (Physicians of the Newcastle-upon-Tyne Region, 1971; Research Committee of the Scottish Society of Physicians, 1971) did not give any data concerning non-cardiovascular deaths.

GENERAL COMMENTS

Clofibrate produced only a modest reduction in the mean serum cholesterol level and this was matched by a similarly modest but significant reduction in the number of IHD events, confined to non-fatal myocardial infarcts. There are a number of factors which might have militated against a more striking preventive effect than shown by this trial.

(1) Reduction of plasma lipids might have been too small.

(2) The partial control of one risk factor might not be expected to produce a significant yield in the face of persistence of other risk factors.

(3) The duration of lipid lowering might not have been long enough to influence long-standing coronary artery disease.

(4) Reduction of plasma lipids might have been started too late in life.

(5) Adherence to treatment might have been incomplete, though plasma levels of clofibrate do not suggest this. It is widely assumed and is part of the basis of many national health education campaigns that a greater reduction in serum cholesterol would be associated with a greater effect on IHD incidence.

But this is difficult to achieve. Unfortunately, there is a sharp division in experience between those who treat patients or individuals through the aegis of a major hospital or lipid clinic, where it is possible to achieve good control of raised plasma lipids, and those who have attempted to control them over long periods in the community. Perhaps it is realistic to conclude that only partial control is readily obtainable in any setting other than one where there is close and regular surveillance, and that this may not be enough.

The excess in total mortality has much concerned us. The mortality from diseases of the liver, biliary tract, and intestines may be a fortuitous association, and, indeed, the number of deaths involved is small, but it could also be due either to clofibrate itself or relate to the effects of the drug in promoting excretion of sterols by way of these tissues. If this speculation is true, the implications for other lipid-lowering regimens are plain. Attention should be paid, therefore, to the possiblity of pathology arising in these tissues with the long-term administration of other regimens that promote excretion of bile sterols.

The investigators are grateful to the men who have participated in this long trial for their willing and patient co-operation.

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The names of technical, computing, and clerical staff are available on request (Addendum F).

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[1]LIST OF ADDENDA AVAILABLE ON REQUEST

A. Clinical data forms and questionnaires
B. Serum cholesterol methods
C. Centre differences
D. Population at risk by 5-year age-group and centre
E. Deaths more than one year out of trial
F. List of technical, computing, and clerical staff

LIST OF APPENDICES

1. Criteria for rejection and withdrawal
2. Statistical methods
3. Definition of end-points
4. Centre differences
5. Drug adherence
6. Conditions not necessarily causing withdrawal but recorded as possible side-effects

APPENDIX 1

CRITERIA FOR REJECTION AND WITHDRAWAL

Rejection from Entry into the Trial

1. History of treated myocardial infarction with ECG signs (see 2a and b below) and/or enzyme changes (using local methods and standards). Previous ECG and hospital records must be examined. An unsubstantiated history of myocardial infarction is not a cause for rejection.

2. ECG evidence of heart disease (Minnesota code system):
   - (a) ECG evidence of myocardial infarction or widespread myocardial ischaemia; i.e. category 1-1, 1-2, 4-1, 5-1, 6-1 or 9-6 (as defined).
   - (b) Complete left bundle branch block: 7-1.
   - (c) "Lone" atrial fibrillation or flutter.
   - (d) Multiple (more than 4 in 12 complexes) or bifocal ventricular extrasystoles.

3. Systemic hypertension:
   - (a) A diastolic blood pressure of 120 or greater on any one occasion.
   - (b) A diastolic blood pressure of 110-119 on any two occasions.
   - (c) A diastolic blood pressure of 110-119 on any one occasion if accompanied by ECG signs of left ventricular hypertrophy, or strain; i.e. 3-1, or 3-3 + 5-2 or + 5-3.
   - (d) If the diastolic blood pressure is within the accepted limits but only on account of treatment with anti-hypertensive drugs and the ECG shows signs of left ventricular hypertroply or strain; i.e. 3-1, or 3-3 + 5-1 or + 5-2 or + 5-3.

4. Clinical evidence of rheumatic heart disease.

5. Congenital heart disease.

6. Pulmonary heart disease - as defined by the World Health Organisation (1961). Chronic bronchitis, emphysema or kyphoscoliosis when associated with ECG signs of right ventricular hypertrophy or strain - 2-2, 3-2 , 7-2 and 7-3.

7. Other heart disease associated with cardiomegaly or heart failure.

8. Diabetes mellitus requiring drug treatment.

9. Co-existing disease with an unfavourable prognosis reducing likelihood of completion of trial:
   - (1) Malignant disease.
   - (2) Residual paralysis due to cerebral damage with or without hypertension.
   - (3) Chronic advanced renal disease with systemic manifestations.
   - (4) Cirrhosis of liver with systemic manifestations.

NOTE: A positive answer to the effort chest pain questionnaire alone or coronary insufficiency (as defined) are not indications for rejection.

Withdrawal after Admission to the Trial

1. Myocardial infarction - see "Definition of end-points" in Appendix 3.

2. Hypertension - as for the criteria for rejection, until November 1973. Thereafter hypertensive men were kept in the trial and treated where necessary.

3. Other heart disease - which has previously not been recognised - as defined under rejection criteria 5, 6 and 7.

4. Diabetes mellitus - requiring drug treatment.

5. Contraindications for taking capsules:
   - (a) Side-effects which cannot be tolerated by individual.
   - (b) Infective hepatitis and cirrhosis.
   - (c) Advanced renal disease.
   - (d) Agranulocytosis or thrombocytopenic purpura.

APPENDIX 2

STATISTICAL METHODS

Incidence and Mortality Rates are expressed per 1000 per annum i.e. as

$$\frac{\text{the number of new events (or deaths)}}{\text{man-years of exposure}} \times 1000$$

Man-years of exposure were calculated separately, for each man, as the time, in years and fractions of a year, from admission to withdrawal from the trial for in-trial rates, and from admission to withdrawal + 1 year for rates of events occurring in the trial or within one year after withdrawal.

Date of Withdrawal was defined as the date of the last trial visit for men who were in the trial when it stopped, but otherwise as the date of the event which removed the man from the trial - e.g. death, myocardial infarction, withdrawal for medical reasons, or of explicitly "opting out". For men who were "lost to follow-up" the date was taken as 9 months from the date of the last trial visit, during the period when visits were at 6-monthly intervals, and as 1½ years from the date of the last trial visit in the period when visits were at 12-monthly intervals. As stated in the text, a similar principle was adopted for deciding whether a death occurred "in the trial" or "out of the trial".

Age-standardisation was by simple averaging of the death-rates in five-year age-groups. "All-centre" rates were standardised over the range 40-59 years, but because there were only 57 men aged 54-59 on admission in Prague (Addendum D), individual centre rates were standardised over the range 40-54 years, thus enabling them to be compared.

This method of standardisation was adopted, after much discussion, as the simplest and clearest way of dealing with a situation made difficult by the difference in age-structure of the trial populations in the several centres. The use of equal weights for the 5-year age-groups corresponded reasonably closely with the age-distributions of the populations from which the men were drawn (as opposed to the trial populations) in each centre. Any more detailed weighting system (e.g. by centre and age distributions of the trial population) would have produced very variable rates in the individual cells and thus high standard errors. This also was one of the main reasons for excluding from the age-standardisation deaths in the range 30-39. The other reason was the absence of any men in Prague in this age-range.

Life Table The life-table data are calculated by standard methods, using intervals of 1 year from admission. The tests of significance between survivorship curves is a χ^2 test with 1 degree of freedom and follows the approach of Mantel (1966) and Cox (1972), using a constant hazard rates model. That is to say it tests the difference between the shapes of the entire curves rather than the percentage surviving at a particular period after admission. In this it is similar to the log-rank test but uses grouped intervals rather than precise times.

The following tables give the percentages free from various events at different stages in the study, calculated on a life-table basis and shown in Figures 2 and 5 or mentioned in the text, together with the standard errors of these rates and the results of the overall tests of significance.

Significance tests · The significance of the difference between the numbers of events in Groups I and II were calculated by the binomial formula on the expectation that they should be equal. Slight differences in numbers exposed to risk were ignored.

In comparing standarised rates the variance of the standardised rate was assumed to be the sum of the variances in the separate 5-year age-groups, appropriately weighted. Thus, for standardisation at ages 40-59, let r_i be the rate and d_i the number of events in age-group i, where i = 1,2,3,4, corresponding to ages 40-44, 45-49, 50-54, 55-59, respectively. The variance of r_i was taken to be approximately r_i^2/d_i. The standardised rate is, thus, $\frac{1}{4}\sum_{i=1}^{4} r_i$

and its variance $\frac{1}{16}\sum r_i^2/d_i$

Formulae for Cholesterol Change Let C_{1x} indicate the serum cholesterol level of a man in Group I at the xth visit, and C_{1p} the mean of his pre-treatment cholesterol levels. Let C_{2x} and C_{2p} be the corresponding values for a man in Group II. Let $\overline{C}_{2x}$ be the mean of the serum cholesterol levels at the xth visit for all men in Group II in the same centre, and $\overline{C}_{2p}$ the corresponding mean of pre-treatment cholesterol levels.

Life Table "Survivorship" Data

The figures are percentages free of the event indicated ± the standard error of this percentage.

Years in Trial	IN-TRIAL								
	All I.H.D.			Fatal I.H.D.			Non-fatal I.H.D.		
	I	II	III	I	II	III	I	II	III
0	100	100	100	100	100	100	100	100	100
1	99.5±0.10	99.4±0.11	99.9±0.05	99.9±0.05	99.9±0.03	99.9±0.03	99.6±0.08	99.5±0.10	99.9±0.04
2	98.9±0.15	98.7±0.16	99.6±0.09	99.7±0.07	99.8±0.06	99.9±0.04	99.1±0.13	98.8±0.15	99.6±0.09
3	98.3±0.19	98.2±0.19	99.3±0.12	99.6±0.09	99.7±0.08	99.9±0.05	98.7±0.16	98.5±0.18	99.5±0.11
4	97.9±0.21	97.3±0.24	99.2±0.13	99.6±0.10	99.6±0.10	99.8±0.07	98.3±0.19	97.8±0.22	99.4±0.12
5	97.3±0.24	96.7±0.27	99.0±0.15	99.5±0.11	99.4±0.11	99.7±0.08	97.9±0.22	97.2±0.24	99.3±0.13
6	96.8±0.27	95.7±0.31	98.8±0.17	99.3±0.13	99.3±0.13	99.7±0.08	97.4±0.24	96.4±0.29	99.0±0.15
7	95.8±0.35	94.8±0.37	98.3±0.23	99.0±0.17	99.2±0.16	99.5±0.14	96.7±0.31	95.6±0.35	98.8±0.19
8	95.1±0.46	94.0±0.50	98.1±0.28	99.0±0.17	99.0±0.21	99.5±0.14	96.0±0.44	94.9±0.46	98.6±0.24

Comparison of Groups	χ^2	P	χ^2	P	χ^2	P
I & II	4.583	< 0.05	0.056	> 0.05	6.173	< 0.05
I & III	52.787	< 0.01	7.280	< 0.01	46.522	< 0.01
II & III	94.363	< 0.01	5.945	< 0.05	94.497	< 0.01

Years since entered Trial	IN-TRIAL + 1 YEAR AFTER LEAVING					
	Total Mortality			Non I.H.D. Mortality		
	I	II	III	I	II	III
0	100	100	100	100	100	100
1	99.7±0.08	99.8±0.05	99.8±0.06	99.8±0.05	99.9±0.04	99.9±0.05
2	99.2±0.13	99.3±0.12	99.7±0.08	99.6±0.09	99.5±0.10	99.7±0.07
3	98.6±0.17	99.0±0.15	99.4±0.12	99.2±0.13	99.3±0.12	99.5±0.10
4	98.3±0.19	98.5±0.18	99.1±0.15	98.9±0.15	99.0±0.14	99.3±0.13
5	97.7±0.22	98.2±0.20	98.6±0.18	98.5±0.18	98.9±0.16	98.9±0.16
6	97.0±0.27	97.6±0.24	98.2±0.21	98.0±0.22	98.4±0.20	98.5±0.20
7	95.7±0.37	96.9±0.30	97.4±0.29	97.1±0.30	98.0±0.24	98.0±0.25
8	95.0±0.47	95.9±0.47	96.5±0.46	96.4±0.43	97.6±0.35	97.3±0.41

Comparison of Groups	χ^2	P	χ^2	P
I & II	4.280	< 0.05	4.553	< 0.05
I & III	17.033	< 0.01	5.849	< 0.05
II & III	4.025	< 0.05	0.082	> 0.05

Then the mean percentage change at the xth visit in all the men in that centre in Group II is

$$\frac{\bar{C}_{2p} - \bar{C}_{2x}}{\bar{C}_{2p}} \text{ X } 100,$$

and the cholesterol change at the xth visit of an individual in Group I is

$$\frac{C_{1p} - C_{1x}}{C_{1p}} \text{ X } 100$$

Thus the man's cholesterol change at visit x as defined in the text is

$$\left[\frac{C_{1p} - C_{1x}}{C_{1p}} - \frac{\bar{C}_{2p} - \bar{C}_{2x}}{\bar{C}_{2p}}\right] 100$$

or

$$\left[\frac{\bar{C}_{2x}}{\bar{C}_{2p}} - \frac{C_{1x}}{C_{1p}}\right] 100$$

The man's mean cholesterol change (or response) is the mean of this function for all the man's visits from the second onwards.

Individual changes in Groups II and III, similarly defined in terms of the mean change in Group II are:-

$$\left[\frac{\bar{C}_{2x}}{\bar{C}_{2p}} - \frac{C_{2x}}{C_{2p}}\right] 100 \quad \text{and} \quad \left[\frac{\bar{C}_{2x}}{\bar{C}_{2p}} - \frac{C_{3x}}{C_{3p}}\right]$$

by obvious extension of the notation to Group III.

Similarily mean changes (over all men at a given centre, at visit x) in Groups I and III were defined as

$$\left[\frac{\bar{C}_{2x}}{\bar{C}_{2p}} - \frac{\bar{C}_{1x}}{\bar{C}_{1p}}\right] 100 \quad \text{and} \quad \left[\frac{\bar{C}_{2x}}{\bar{C}_{2p}} - \frac{\bar{C}_{3x}}{\bar{C}_{3p}}\right] 100$$

respectively.

Mean In-trial Cholesterol Level The mean level (for all men in a treatment Group at a given centre and visit) in Groups I and III was derived by applying to the mean pre-treatment level the mean percentage change figure, derived as above to allow for changes in the average value of cholesterol levels from time to time in Group II. For Group II the observed levels were used. These values were then averaged over all visits to give a mean in-trial cholesterol level for that Group and centre.

In order to be able to use the same scale of cholesterol values a further correction was made to adjust for initial differences between centres in the pre-treatment cholesterol levels. (As has been stated, the results of the exchange of serum samples shows that differences between centres in observed values were mainly methodological.)

This correction was made as follows:-
A single factor, f, was derived for each of the two centres (Budapest and Prague) relating its mean values to those for Edinburgh.

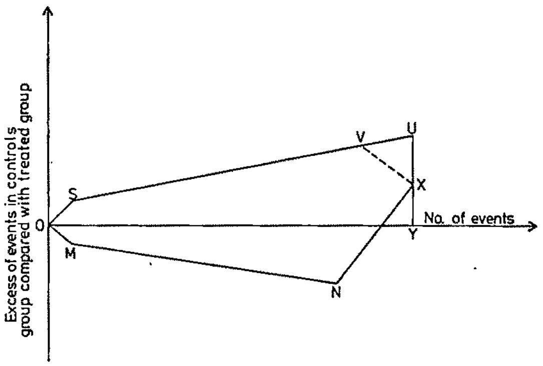
$$f = \frac{2x_1 + x_3}{2y_1 + y_3}$$

where x_1, y_1 = are the mean pre-treatment levels, at ages 40-59 for the combined Groups I and II for the centre (x_1) and for Edinburgh (y_1)

and x_3, y_3 = are the mean pre-treatment levels, at ages 40-59 for Group III for the centre (x_3) and for Edinburgh (y_3)

The values of f were 0.948 for Budapest and 0.874 for Prague and were used throughout to convert centre values to a common scale where this was required - e.g. in Figure 4, or in the multivariate analysis. These figures were also used to denote the "all centres" figures in the bottom line of Table 7.

Sequential Scheme for Monitoring of Results It was agreed that the results of the trial should be released to the principal investigators if, according to the sequential diagram in Appendix 2, Figure 1, a path crossed the line SVX indicating a result in favour of the treatment: or if one crossed the line MN, the early warning line, indicating a result against the treatment or if a line crossed NX representing a non-significant result. Any of these would be reported in the first instance to the Committee of Principal Investigators who would decide, on the basis of this and other information, whether the result should be further divulged and whether the trial should be stopped. This scheme applied to any class of event - e.g. all deaths, deaths from ischaemic heart disease, I.H.D., or any adverse side-effect.


Excess of events in controls group compared with treated group
No. of events
O
S
M
N
V
U
X
Y

Appendix 2: Fig. 1 *Excess of events in control group compared with treated group.*

The line SVU is taken from Armitage's set of closed sequential designs (Armitage, P. 1957, Biometrika, 44, 9-26) with $2\alpha = 0.01$, $\beta = 0.90$ and set to detect a 1.5:1 difference. The line MN is taken from the same set of designs, but with $2\alpha = 0.10$, $\beta = 0.90$ and set to detect the same difference. The point Y is set at 400 events, chosen to give a fixed sample result with $2\alpha = 0.01$ and $\beta = 0.90$ and able to detect a 1.5:1 difference and X is the point on the line YU such that any path which cuts YU above X gives a significant result. VX is at 45° to the vertical so that any path which cuts VX must cut YU above X. XN is also at 45° to the vertical so that no path which cuts NX can cut YU above X (and thus give a significant result).

The characteristics of this scheme are as follows:

(1) Effective (two-sided) significance level for a favourable result - 1.4% (347).

(2) Effective (two-sided) significance level for an unfavourable result - 9.4% (347).

(3) Power to detect an actual reduction of 33% in incidence in the treated group - 93% (218).

(4) Power to detect an unfavourable result of the same magnitude - 91% (110).

The figures in brackets are the median number of events required before a decision is reached (Heady, 1974).

Multivariate Analysis

The multiple logistic model was used (Walker & Duncan, 1967) the end-points being either any episode of major I.H.D., of non-fatal myocardial infarction or of fatal I.H.D., or death from causes other than I.H.D.

The following variables were used in the equations:

Variable	Units
Log$_e$ (age)	Log (years)
Smoking	0 = never or ex- 1 = present
Father alive/dead	0 = alive 1 = dead
Treatment	1 = control (Group II only) 2 = clofibrate
Systolic blood pressure	mmHg
Corrected mean pre-treatment Cholesterol (defined in text)	mg/dl
Mean cholesterol change (defined in text)	percent

Except for the last, all these variables refer to entry characteristics.

In addition, the following variables were also examined in various combinations: age, number of cigarettes smoked, whether the subject's mother was alive, presence of I.H.D. in siblings, weight, height, diastolic blood pressure, presence of basal or apical heart murmur, arcus senilis, xanthelasma, xanthoma tuberosum, triceps and subscapular skinfold thickness, Quetelet index and positive chest-pain questionnaire, but their contribution to prediction was either non-significant or less than that of the selected variables (e.g. in the case of highly correlated measurements such as systolic and diastolic blood pressure).

The Table gives details of the coefficients (β), t value, standardised (β), and intercepts (α) fitted to the multiple logistic equations for the relationships between some or all of the main variables and various end-points in various treatment groups. The statistical significance of any coefficient is indicated by the "t" value (roughly, if t is greater than 2, or less than -2, the coefficient may be regarded as significant at the 5% level). To take account of the different units used in comparing results with other studies and in assessing the relative importance of the variables in any one equation standardised β's should be used. They are derived by multiplying the β's by the standard deviation of the variables. In Tables 8 and 10, comparisons (e.g. between different sub-groups of high and low levels of 'risk' factors) have been based on the 'expected' incidence of events for a given set of baseline characteristics using the data derived from GroupII. Thus, for example, the expected probability of an individual experiencing (over the duration of the study) a given event (e.g. any I.H.D.), based on the data from Group II, would use the coefficients and intercept shown at No. 1 of the Table. The sum of such 'risk scores' for each individual in any group or sub-group, provides an estimate of the total number of specified events to be expected from the independent contributions of each of the baseline characteristics. This figure, because of the exponential distribution of individual risk scores, (and the iterative fitting procedure), overestimates (by 3-5%) the true incidence, and derived values have been corrected accordingly.

In the example quoted above, the calculated 'risk score' for I.H.D. of two individuals with the following baseline characteristics:

	Age	Smoking	Father	Systolic BP	Cholesterol
A:	40	0	Alive	125	220
B:	55	+	Dead	160	260

would be:- $p(A) = 0.0072$

$p(B) = 0.1324$

Where $p = \dfrac{1}{1 + e^{-(\alpha+\Sigma\beta_i x_i)}}$

x_i = value for each of i baseline characteristics

β_i = regression coefficient for baseline characteristic x_i

α = Intercept

In this (very limited) example the sum of the risk scores (which should be multiplied by the appropriate factor) gives the (uncorrected) expected total number of events (0.1396) expected to occur if there had been no effect of intervention.

Results from other studies

The unstandarised coefficients (β) for serum cholesterol in multivariate equations for the "prediction" of ischaemic heart disease from three other published studies are given below. In each study, men previously free of ischaemic heart disease have been followed for a number of years. These coefficients should be compared with the corresponding value from the first line of the Table in this Appendix. i.e, 0.008.

	Age range	β
Seven country study (Keys et al., 1972)	40-59	0.010
Israel (Medalie et al., 1973)	40-49	0.014
	50-59	0.007
Framingham (Kannel et al., 1964)	40-62	0.008

A cholesterol reduction of 9% (the mean value observed in this study) would correspond to a reduction of 20% in the incidence of I.H.D. if β is 0.10, to 16% if β is 0.008, and to 24% if β is 0.014.

It will be seen that the range of values of β quoted above is similar to the range seen in the first 7 lines of the Table in this Appendix where the equations for different combinations of treatment groups and variables included in the equations are shown.

Acknowledgement

The help and advice of Mr. David Clayton lately of the Department of Clinical Epidemiology and Social Medicine of the Royal Free Hospital School of Medicine in connection with the technical aspects of the life-table and multivariate analysis is gratefully acknowledged. The test of significance in the life table analysis was developed by him, and he wrote the associated computer programme as well as the programme to handle the multivariate analysis. In both respects his statistical advice was also invaluable.

No.	End-point	Group(s)	β, (t-value) and standardised β for variables							Intercept
			Log_e(Age) (log(yrs))	Smoking (0/1)	Father History (0/1)	Systolic BP (mmHg)	Cholesterol (mg/dl)	Cholesterol Change (%)	Treatment (1/2)	
1	All I.H.D.	II	2.76 (4.4) 0.40	0.87 (5.3) 0.43	0.48 (2.1) 0.21	0.014 (3.7) 0.25	0.0084 (3.4) 0.22	/	/	-18.707
2	All I.H.D.	III	5.21 (4.4) 0.85	1.08 (3.6) 0.54	-0.03 (-0.1) -0.01	0.018 (2.8) 0.31	0.017 (1.6) 0.21	/	/	-29.416
3	All I.H.D.	I	3.32 (4.5) 0.48	0.79 (4.3) 0.39	0.88 (3.0) 0.38	0.0064 (1.4) 0.11	0.011 (4.6) 0.29	/	/	-21.042
4	All I.H.D.	II/III	3.40 (6.1) 0.53	0.94 (6.5) 0.47	0.35 (1.8) 0.16	0.0153 (4.6) 0.23	0.012 (8.1) 0.51	/	/	-22.292
5	All I.H.D.	I/II	3.09 (6.1) 0.44	0.83 (6.5) 0.41	0.67 (3.6) 0.29	0.0126 (4.2) 0.22	0.010 (5.1) 0.27	0.023 (3.9) 0.24	/	-20.430
6	All I.H.D.	I/II	3.00 (6.3) 0.44	0.83 (6.8) 0.41	0.64 (3.6) 0.28	0.011 (3.7) 0.19	0.0095 (5.6) 0.26	/	-0.32 (-2.9) 0.16	-19.282
7	All I.H.D.	I/II	3.09 (6.1) 0.22	0.84 (6.5) 0.21	0.67 (3.6) 0.29	0.013 (4.2) 0.22	0.0099 (5.0) 0.26	0.019 (3.0) 0.20	-0.18 (-1.4) -0.09	-20.145
8	Non-fatal M.I.	II	2.02 (3.0) 0.29	0.89 (4.9) 0.44	0.71 (2.8) 0.31	0.014 (3.3) 0.24	0.0072 (2.6) 0.19	/	/	-15.875
9	Fatal I.H.D.	II	7.46 (4.1) 1.07	0.80 (2.1) 0.40	-0.64 (-1.4) -0.28	0.015 (1.7) 0.26	0.013 (2.5) 0.33	/	/	-39.128
10	Non-I.H.D. Deaths (in- and<1 yr ex-trial)	III	6.79 (5.8) 1.11	0.72 (2.8) 0.36	0.28 (0.8) 0.13	0.010 (1.6) 0.17	-0.012 (-1.8) -0.23	/	/	-30.347
11	Non-I.H.D. deaths (in- and<1 yr ex-trial)	III	6.88 (6.1) 1.13	0.70 (2.7) 0.35	/	0.0099 (1.5)	/	/	/	-32.472
12	Non-I.H.D. deaths (in- and<1 yr ex-trial)	III	7.10 (6.4) 1.16	/	/	/	/	/	/	-31.576

APPENDIX 3

DEFINITION OF END-POINTS OF VASCULAR DISEASES

Ischaemic heart disease

The term ischaemic heart disease (I.H.D.) as used in the trial comprises major and minor events defined as follows:

A. Major Events

(1) Fatal events – these include deaths from myocardial infarction (as defined below) and deaths where it is not possible with certainty to diagnose myocardial infarction, but surrounding circumstances suggest that this is the cause.

Fatal events have been sub-divided into those occurring within 3 hours of the onset of symptoms, and those occurring between 3 hours and 28 days of the onset of symptoms

(2) Non-fatal myocardial infarction (see below) surviving more than 28 days.

(3) Acute coronary insufficiency (see below) surviving more than 28 days. These were classified with non-fatal myocardial infarction in the final analysis.

B. Minor Events

(1) Angina pectoris (see below) with an abnormal ECG (Minnesota codes 4.1, 4.2, 5.1, 5.2, 6.1, 6.2, 7.1, 8.3, 11.1, 12.1, 14.1).

(2) Angina pectoris without one of the above codable abnormalities.

(3) An abnormal ECG (as defined above) developing during the course of the trial without symptoms of chest pain to warrant classification by questionnaire as angina pectoris.

Myocardial infarction

Myocardial infarction was considered to have occurred when:

(1) The resting ECG developed Q-wave changes, classified by the Minnesota code as 1.1 or 1.2, or 9.6 (a new category defined as follows: ST junction (J) and ST segment elevation of 1mm or more with an upward sloping ST segment and a negative or diphasic T wave, with the negative phase of at least 1mm. These changes must be present in at least two leads from V_2-V_6 and last for at least 3 days. The changes described were regarded as indicating recent intramural anterior myocardial infarction).

OR

(2) The resting ECG developed equivocal Q-wave changes (codable as 1.3) with elevated serum enzymes or with classical symptoms (prolonged chest pain of ½ hour or more, acute breathlessness or syncope).

OR

(3) There was a typical clinical picture with classical symptoms (see above) and elevated serum enzymes, but without definite ECG evidence. Consensus had to be reached on these cases at the Annual Review Meeting.

Elevated serum enzymes

These were interpreted in each centre according to the locally accepted ranges of normal and abnormal.

Acute coronary insufficiency

This was defined as classical chest pain lasting more than ½ hour at rest, with ECG abnormalities codable as 4.1, 5.1 or 7.1, but without elevation of serum enzymes.

Angina pectoris

This was said to be present when appropriate positive answers were given to item 23, "effort chest pain", on the follow-up form. (It was notifiable as newly arising in the trial only if the corresponding questions on the admission form were negative.) The answers to question 23 were said to be positive when positive answers were given to the first or second questions, "Have you ever had any pain or discomfort in your chest?" or "Have you ever had any pressure or heaviness in your chest?" and the third question, "Do you get any of these when you walk uphill or hurry?" In addition the following questions must have been completed in the manner shown below:-

(1) What do you do if you get it while you are walking?
Answer: stop or slow down.
(2) If you stand still what happens to it?
Answer: relieved.
(3) How soon?
Answer: 10 minutes or less.
(4) Will you show me where it is/was?
Answer: sternum (upper middle), sternum lower, left anterior chest plus left arm.

Exercise ECG

This was conducted on a bicycle ergometer using graded work loads of 50, 100 and 150 watts, each of 4 minute duration, according to W.H.O. standards.

An exercise test was done in all cases of angina (positive effort chest pain questionnaire) with normal resting ECG. An intra-exercise ECG was said to be positive if the horizontal or downward sloping segment was depressed 2mm or more; a post-exercise ECG was considered positive when codable as 11-1, 12-1 or 14-1 at any time in the period of 1 to 10 minutes after the test had been stopped. Intra- or post-exercise ECG's were also considered positive if extrasystoles appeared exceeding 10% of the number of observed complexes (based on all ECG readings during the exercise test).

Intermittent claudication

This was said to be present when appropriate positive answers were given to item 24, "leg pain", on the follow-up form (Addendum A). (It was notifiable as newly arising in the trial only if the corresponding questions on the admission form were negative.)

Hypertension

This was defined as:

(a) A diastolic blood pressure of 120 or greater on any one occasion.

(b) A diastolic blood pressure of 110-119 on any two occasions.

(c) A diastolic blood pressure of 110-119 on any one occasion if accompanied by ECG signs of left ventricular hypertrophy or strain (coded as 3.1, or 3.3 + 5.2, or as 3.3 + 5.3).

Cerebrovascular disease

No trial definitions were specified. Centres used their own conventions.

APPENDIX 4 CENTRE DIFFERENCES (See Table 3)

Incidence of Major Ischaemic Heart Disease (IHD), Non-fatal and Fatal, by Age at Entry

Rates per 1000 per annum

Edinburgh

Event	Age at Entry (years)	Group I		Group II		Group III	
		Clofibrate		High Cholesterol Control		Low Cholesterol Control	
		No.	Rate	No.	Rate	No.	Rate
All Major IHD	30-	1	1.0	3	3.0	0	0.0
	35-	6	3.7	6	3.3	2	1.0
	40-	5	2.4	18	8.3	3	1.6
	45-	14	7.1	18	9.7	6	3.4
	50-	11	9.7	5	4.0	10	10.6
	55-	13	14.0	9	12.2	5	9.3
	Total	50	5.7	59	6.7	26	2.9
	St.40-54(a)		6.4		7.3		5.2
Non-Fatal Myocardial Infarction	30-	0	0.0	3	3.0	0	0.0
	35-	5	3.1	6	3.3	0	0.0
	40-	4	1.9	16	7.4	0	0.0
	45-	10	5.1	16	8.6	5	2.9
	50-	9	7.9	4	3.2	8	8.5
	55-	8	8.6	8	10.8	4	7.4
	Total (b)	36	4.1	53	6.0	17	1.9
	St.40-54		5.0		6.4		3.8
Fatal IHD	30-	1	1.0	0	0.0	0	0.0
	35-	1	0.6	0	0.0	2	1.0
	40-	1	0.5	2	0.9	3	1.6
	45-	4	2.0	2	1.1	1	0.6
	50-	2	1.8	1	0.8	2	2.1
	55-	5	5.4	1	1.4	1	1.9
	Total	14	1.6	6	0.7	9	1.0
	St.40-54		1.4		0.9		1.4
Of these: Deaths within 3 hours(c)		8	0.9	4	0.5	4	0.4

(a) Standardised rates for the three age-groups 40-44, 45-59, 50-54, equal weights being given to each age-group.

(b) Includes 4 with Acute Coronary Insufficiency (Intermediate Coronary Syndrome), 2, 2 and 0 in Groups I, II and III respectively.

(c) The numbers of IHD deaths occurring from 3-12 hours were 1, 1, 2, in the three Groups respectively.

APPENDIX 4 CENTRE DIFFERENCES (See Table 3)

Incidence of Major Ischaemic Heart Disease (IHD), Non-fatal and Fatal, by Age at Entry

Rates per 1000 per annum

Budapest

Event	Age at Entry (years)	Group I		Group II		Group III	
		Clofibrate		High Cholesterol Control		Low Cholesterol Control	
		No.	Rate	No.	Rate	No.	Rate
All Major IHD	30-	2	2.9	0	0.0	2	1.4
	35-	2	1.9	1	0.8	1	0.7
	40-	4	2.1	1	0.5	1	0.6
	45-	9	4.3	11	5.1	2	1.2
	50-	6	4.3	15	10.6	2	1.7
	55-	17	9.7	21	12.2	3	2.3
	Total	40	4.5	49	5.5	11	1.2
	St.40-54(a)		3.6		5.4		1.2
Non-Fatal Myocardial Infarction	30-	2	2.9	0	0.0	2	1.4
	35-	1	1.0	1	0.8	1	0.7
	40-	4	2.1	1	0.5	0	0.0
	45-	5	2.4	6	2.8	2	1.2
	50-	6	4.3	12	8.5	2	1.7
	55-	14	8.0	14	8.1	2	1.5
	Total(b)	32	3.6	34	3.8	9	1.0
	St.40-54		2.9		3.9		1.0
Fatal IHD	30-	0	0.0	0	0.0	0	0.0
	35-	1	1.0	0	0.0	0	0.0
	40-	0	0.0	0	0.0	1	0.6
	45-	4	1.9	5	2.3	0	0.0
	50-	0	0.0	3	2.1	0	0.0
	55-	3	1.7	7	4.1	1	0.8
	Total	8	0.9	15	1.7	2	0.2
	St.40-54		0.6		1.5		0.2
Of these: Deaths within 3 hours(c)		5	0.6	6	0.7	2	0.2

(a) Standardised rates for the three age-groups 40-44, 45-49, 50-54, equal weights being given to each age-group.

(b) Includes 7 with Acute Coronary Insufficiency (Intermediate Coronary Syndrome) 2, 4 and 1 in Groups I, II and III respectively.

(c) The numbers of IHD deaths occurring from 3-12 hours were 1, 3, 0, in the three Groups respectively.

APPENDIX 4 CENTRE DIFFERENCES (See Table 3)

Incidence of Major Ischaemic Heart Disease (IHD), Non-fatal and Fatal by Age at Entry

Rates per 1000 per annum

Prague

Event	Age at Entry (years)	Group I		Group II		Group III	
		Clofibrate		High Cholesterol Control		Low Cholesterol Control	
		No.	Rate	No.	Rate	No.	Rate
All Major IHD	30-	0	0.0	0	0.0	0	0.0
	35-	0	0.0	0	0.0	0	0.0
	40-	10	4.3	12	5.6	4	2.0
	45-	38	6.7	55	9.8	10	2.0
	50-	27	11.0	33	13.5	10	4.2
	55-	2	19.5	0	0.0	1	9.8
	Total	77	7.3	100	9.7	25	2.6
	St.40-54 [a]		7.3		9.6		2.7
Non-Fatal Myocardial Infarction	30-	0	0.0	0	0.0	0	0.0
	35-	0	0.0	0	0.0	0	0.0
	40-	8	3.5	11	5.1	4	2.0
	45-	33	5.8	50	8.9	7	1.4
	50-	20	8.1	26	10.6	8	3.4
	55-	2	19.5	0	0.0	1	9.8
	Total [b]	63	5.9	87	8.4	20	2.1
	St.40-54		5.8		8.2		2.3
Fatal IHD	30-	0	0.0	0	0.0	0	0.0
	35-	0	0.0	0	0.0	0	0.0
	40-	2	0.9	1	0.5	0	0.0
	45-	5	0.9	5	0.9	3	0.6
	50-	7	2.8	7	2.9	2	0.8
	55-	0	0.0	0	0.0	0	0.0
	Total	14	1.3	13	1.3	5	0.5
	St.40-54		1.5		1.4		0.5
Of these: Deaths within 3 hours [c]		10	0.9	7	0.7	2	0.2

(a) Standardised rates for the three age-groups 40-44, 45-49, 50-54, equal weights being given to each age-group.

(b) Includes 27 with Acute Coronary Insufficiency (Intermediate Coronary Syndrome) 14, 10 and 3 in Groups I, II and III respectively.

(c) The numbers of IHD deaths occurring from 3-12 hours were 2, 2, 1 in the three Groups respectively.

APPENDIX 4 CENTRE DIFFERENCES (See Table 12)

Deaths in the Trial and within 1 year of leaving it

Main Cause Groups. Numbers of Deaths at Ages 30-59 and

Age-standardised Rates per 1000 per annum at ages 40-54

Cause of Death	Centre	Group I		Group II		Group III	
		Clofibrate		High Cholesterol Control		Low Cholesterol Control	
		Number (All ages)	Rate (40-54)	Number (All ages)	Rate (40-54)	Number (All ages)	Rate (40-54)
Ischaemic Heart Disease	Edinburgh	18	1.6	12	1.4	9	1.2
	Budapest	13	1.0	18	1.3	5	0.7
	Prague	23	2.0	18	1.5	6	0.5
Other Vascular	Edinburgh	1	0.0	6	0.5	1	0.2
	Budapest	7	1.0	3	0.2	5	0.6
	Prague	6	0.4	5	0.6	3	0.2
Neoplasm: malignant	Edinburgh	12	1.5	12	1.0	9	0.6
	Budapest	24	2.9	14	1.1	14	1.8
	Prague	22	1.9	16	1.2	18	1.5
Neoplasm: benign	Edinburgh	1	-	-	-	1	-
	Budapest	-	-	-	-	-	-
	Prague	2	-	-	-	-	-
Other Medical Causes	Edinburgh	2	0.0	1	0.1	0	0.0
	Budapest	8	0.5	2	0.2	1	0.2
	Prague	6	0.6	2	0.2	6	0.5
Accidents & Violence	Edinburgh	5	0.4	1	0.1	1	0.0
	Budapest	8	0.9	6	0.8	9	1.3
	Prague	4	0.3	11	1.0	5	0.4
All causes other than I.H.D.	Edinburgh	21	2.0	20	1.8	12	0.8
	Budapest	47**	5.3	25**	2.3	29	3.9
	Prague	40	3.4	34	3.0	32	2.8
All causes other than I.H.D., Vascular and Accidents & Violence	Edinburgh	15	1.6	13	1.2	10	0.6
	Budapest	32*	3.4	16*	1.3	15	2.0
	Prague	30	2.7	18	1.5	24	2.1
TOTAL ALL CAUSES	Edinburgh	39	3.6	32	3.2	21	2.0
	Budapest	60	6.3	43	3.5	34	4.6
	Prague	63	5.4	52	4.5	38	3.2

* Significant difference between Groups I and II ($P<0.05$).

** Significant difference between Groups I and II ($P<0.01$).

APPENDIX 5

Drug Adherence Group I

(i) Average concentrations of Clofibrate (CPIB) (μg/ml)

Centre	Years in trial				
	1	2	3	4	5
Edinburgh	142	141	151	157	-
Budapest	132	141	134	129	124
Prague	156	165	159	171	171

(ii)

Centre	Percentage of negative estimates in:	
	Men with a major I.H.D. event	All men
	%	%
Edinburgh	3	6
Budapest	12	6
Prague	13	9

(iii) Average concentrations of clofibrate (CPIB)

	Centre	Visit number						
		2	3	4	5	6	7	8
Men with a major IHD event (value at visit immediately preceding IHD event).	Edinburgh	172	145	158	132	154	145	150
	Budapest	128	135	116	160	144	114	91
	Prague	148	145	156	159	141	166	164
All men	Edinburgh	129	142	142	141	151	157	157
	Budapest	132	132	125	141	134	129	124
	Prague	151	156	140	165	159	171	171

APPENDIX 6

Conditions not necessarily causing withdrawal from the trial but recorded as possible side effects

Condition	Edinburgh			Budapest			Prague			All Centres			
	I	II	III	I	II	III	I	II	III	I	II	III	Total
Endocrine, Metabolic Diseases													
Weight gain	66**	24**	36	25	15	13	8	2	1	99**	41**	50	190
Mental Disorders													
Impotence	13	7	14	18	16	7	27**	10**	10	58**	33**	31	122
Diseases of Circulatory Sys.													
Cardiac Arrhythmia	–	–	2	–	–	–	–	–	–	–	–	2	2
Diseases of Respiratory Sys.													
Catarrh, coryza	2	2	2	–	–	–	–	–	–	2	2	2	6
Diseases of Digestive System													
Aggravation of peptic ulcer	–	–	1	–	–	–	–	–	–	–	–	1	1
Indigestion, abdom. symptoms	168	163	119	43*	23*	21	109**	55**	59	320**	241**	199	760
Constipation	20	19	24	5	4	1	3	3	2	28	26	27	81
Intestinal hurry	130**	90**	121	9	16	13	31	20	23	170*	126*	157	453
Diseases of the Skin													
Pruritus	2	–	–	6	5	4	4	–	3	12	5	7	24
Alopecia	2	2	1	1	1	1	–	–	–	3	3	2	8
Hirsutism	1	–	–	–	–	–	–	–	–	1	–	–	1
Symptoms & Ill-defined Conditions													
Dizziness	7	6	7	6	4	12	3	7	5	16	17	24	57
Sleep Disturbance	6	2	4	7	7	6	8	11	4	21	20	14	55
Ocular symptoms	–	2	–	–	–	–	–	–	–	–	2	–	2
Dental symptoms	1	1	–	–	–	–	–	–	–	1	1	–	2
Paraesthesia	2	6	5	6	7	12	6	5	8	14	18	25	57
Epistaxis	15	18	21	1	3	1	6	2	2	22	23	24	69
Chest discomfort	1	2	–	–	–	–	–	–	–	1	2	–	3
Anorexia	1	1	2	–	–	–	–	–	–	1	1	2	4
Nausea	2	–	1	–	–	–	–	–	–	2	–	1	3
Urinary symptoms	3	1	3	6	3	–	1	–	1	10	4	4	18
Muscular cramps	10	7	5	4	5	4	3	2	–	17	14	9	40
Arthralgia	1	7	5	–	–	1	3	3	2	4	10	8	22
Hyperhidrosis	24**	7**	7	4	7	3	1	3	–	29	17	10	56
Rash	29	24	21	9	12	5	16	12	17	54	48	43	145
Increased appetite, thirst	7	3	2	8	2	10	7	2	2	22	7	14	43
Fatigue, depression	31	30	24	7	5	5	13	13	11	51	48	40	139
Headache	4	4	6	9	6	1	2	3	11	15	13	18	46
Coldness	8	10	6	2	3	–	–	1	–	10	14	6	30
Reduced tolerance to alcohol	2	6	6	–	1	2	–	–	–	2	7	8	17
Other	–	–	–	–	1	–	–	–	–	–	1	–	1

* Significant difference between Groups I and II ($P < 0.05$).

** Significant difference between Groups I and II ($P < 0.01$).

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Gaps in anterograde conduction in patients with the short PR interval, normal QRS complex syndrome

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SUMMARY Of 8 patients with the short PR interval, normal QRS complex syndrome studied recently, 3 reported here displayed gaps in anterograde conduction. Atrial premature beats at decreasing coupling intervals conducted with minimal AH prolongation until a zone within the cardiac cycle was reached where conduction failed at a supra-Hisian level. Conduction resumed at earlier atrial coupling intervals and was associated with a sudden increase in the AH interval and the appearance of atrial echo beats with earliest atrial activation on the proximal coronary sinus electrogram.

It is suggested that the failure of anterograde conduction at relatively late atrial coupling intervals was caused by a short AH functional refractoriness produced by the pre-excitation of the lower AV junction by a partial AV nodal bypass. Conduction resumed only when early atrial premature beats found the extranodal pathway refractory and were transmitted with decremental delay through the AV node.

Inhomogeneity of refractoriness along the length of the atrioventricular (AV) transmission system may lead to gaps in anterograde conduction (Moe *et al.*, 1965) where an atrial premature beat within a limited zone of the cardiac cycle fails to conduct anterogradely but both earlier and later atrial systoles conduct normally (Wit *et al.*, 1970a). An early hypothesis (Durrer, 1968) suggested that such 'gap phenomena' might be explained by functional longitudinal duality of conduction at a site proximal to the location of conduction block during the gap. Many examples of gap phenomena have been described (Damato *et al.*, 1976), but their explanation has not required the hypothesis of proximal dual conduction.

The syndrome of short PR interval, normal QRS complex associated with paroxysms of tachycardia (Clerc *et al.*, 1938; Lown *et al.*, 1952) provides an example of dual conduction pathways at AV nodal level (Denes *et al.*, 1974b) which is often associated with gaps in anterograde conduction (Seipel *et al.*, 1976). In this study the interplay between dual proximal conduction and distal conduction failure in 3 patients with the short PR interval, normal QRS complex syndrome is defined.

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Patients and methods

During the months of March to July 1977, 8 patients with the short PR interval, normal QRS complex syndrome were admitted for electrophysiological study. Of the 8 patients, 3 had anterograde conduction gaps and their clinical details are listed in Table 1. All 3 patients had PR intervals ⩽ 0·12 s and QRS complexes < 0·10 s. Two patients presented with repeated paroxysms of supraventricular tachycardia and the third patient suffered frequent attacks of atrial fibrillation with a rapid (180 to 240 beats per minute) ventricular response. There was no evidence of any underlying cardiac pathology or intercurrent disease in any of these patients.

Electrophysiological studies were performed in the non-sedated, post-absorptive state in the supine

Table 1 *Clinical and electrocardiographic data*

Case	*Age*	*Sex*	*PR*	*QRS duration*	*QRS frontal axis*	*Presentation*
1	50	M	0·12 s	0·09 s	+60°	Paroxysmal SVT
2	20	M	0·11 s	0·07 s	+75°	Paroxysmal SVT
3	33	M	0·12 s	0·09 s	+40°	Paroxysmal AF

SVT, supraventricular tachycardia; AF, atrial fibrillation.

position. All medications had been withdrawn at least 4 days before the study. Bipolar electrode catheters with 1 cm interelectrode distance were introduced percutaneously via the right femoral vein and positioned in the high right atrium, against the septal leaflet of the tricuspid valve and in the apex of the right ventricle. A quadripolar electrode catheter with 1 cm electrode separations was passed via a left brachial vein into the coronary sinus. Recordings were made from the distal and proximal bipoles. All signals were filtered between 50 and 700 Hz and recorded simultaneously with three surface leads: I, aVF, and V1, on an Elema Mingograf recorder. Time markings at 1 second intervals were superimposed on an oscillating 50 Hz baseline. Stimulation was performed with a Devices 4270 stimulator which delivered square wave pulses of 1·5 ms duration at an amplitude approximately twice the diastolic threshold. Signals were recorded during sinus rhythm and during incremental atrial pacing at rates between 100 and 160 beats per minute. Anterograde conduction characteristics were assessed by the atrial extrastimulus method in which a programmed atrial premature beat was introduced after a sequence of 8 regularly paced atrial systoles. Anterograde conduction studies were performed at several different basic pacing rates and after the intravenous infusion of 0·1 mg per kg body weight of verapamil.

DEFINITIONS

The following abbreviations, terms, and definitions are used throughout the text:

A_1, H_1, V_1: The atrial, His bundle, and ventricular electrogram during basic atrial pacing.

A_2, H_2, V_2: The atrial, His bundle, and ventricular electrograms produced by premature atrial stimulation.

PA: The interval between the earliest atrial activation and the intrinsic deflection of the atrial electrogram on the His bundle electrode.

AH: The interval between the intrinsic deflection of the atrial electrogram and the intrinsic deflection of the His bundle electrogram on the His bundle electrode.

HV: The interval between the intrinsic deflection of the His bundle electrogram and the earliest ventricular activation on any lead.

Anterograde conduction curve (Moe *et al.*, 1956): A graphic representation of the results of the atrial extra-stimulus technique where H_1H_2 and V_1V_2 intervals are plotted against their corresponding A_1A_2 values.

Fast (atrionodal) pathway ERP: Effective refractory period of the fast extranodal conduction pathway defined, in this report, as the shortest A_1A_2 value before the occurrence of slow pathway conduction. This interval is the lower limit of the anterograde gap in conduction during which it is assumed that concealed fast pathway conduction continues.

Fast (atrionodal) pathway FRP: Functional refractory period of the fast extranodal pathway defined as being equal to the effective refractory period of this pathway. Extranodal fibres of the type described by James (1963) or Brechenmacher (1976) are composed of atrial myocardium or Purkinje-like tissue which ordinarily does not possess decremental conduction characteristics at longer coupling intervals of A_1A_2. A definition which involved H_1H_2 measurements would include final common pathway conduction between the site of insertion of the extranodal pathway and the point from which the His bundle deflections were recorded.

Slow (AH) pathway ERP: Effective refractory period of the slow AH conduction pathway defined as the longest A_1A_2 interval (not including A_1A_2 intervals during the anterograde gap) which is not conducted to the His bundle.

Slow (AH) pathway FRP: Functional refractory period of the slow AH conduction pathway defined as the shortest H_1H_2 interval achieved by any A_1A_2 value shorter than the ERP of the fast pathway.

Anterograde gap: A range of A_1A_2 values within the cardiac cycle where A_2 does not result in a ventricular response bracketed by zones of intact conduction.

Atrial echo zone: A range of A_1A_2 intervals in which A_2 results in a second atrial response (Ae) in which the earliest atrial activation occurs on the proximal coronary sinus electrogram.

Results

Conduction intervals during sinus rhythm are listed in Table 2. All 3 patients had short AH times ($\leqslant$ 60 ms) but normal intra-atrial (PA = 20-50 ms) and specialised intraventricular (HV = 35-50 ms) conduction times. Incremental atrial pacing (Table 2) resulted in little or no AH prolongation.

Anterograde conduction characteristics (Fig. 1) as assessed by the atrial extrastimulus technique were abnormal in 3 respects: (1) atrial premature stimuli at progressively shorter coupling intervals resulted in minimal prolongation of the A_2H_2 time, until (2) total anterograde block developed, in all but one instance above the site from which the His bundle deflection was recorded, and (3) conduction resumed at shorter intervals of A_1A_2 with a sudden increase of the A_2H_2 interval and the simultaneous appearance of atrial echo beats or sustained tachycardia.

Recordings from case 2 are illustrated in Fig. 2.

Table 2 *Conduction intervals during sinus rhythm and incremental atrial pacing*

Case	*Sinus rhythm*			*Atrial pacing*	
	PA	*AH*	*HV*	*100 bpm AH*	*160 bpm AH*
1	30	55	35	55	60
2	25	45	40	45	45
3	20	60	40	60	70

Basic atrial pacing at a cycle length of 545 ms resulted in an A_1H_1 interval of 45 ms and an H_1V_1 interval of 40 ms. The QRS morphology throughout the study was that of right bundle-branch block. A_1A_2 intervals above 350 ms did not produce A_2H_2 prolongation, but as the A_1A_2 interval was reduced to 310 ms the A_2H_2 interval increased to 80 ms and anterograde block occurred below the level of the His bundle. At an extrastimulus coupling interval of 300 ms block occurred at a supra-Hisian level. Conduction resumed at an A_1A_2 interval of 260 ms with an A_2H_2 interval of 185 ms and an atrial echo beat with earliest atrial activation on the proximal coronary sinus electrogram. Further reduction in the A_1A_2 interval resulted in conduction to the ventricles with appropriate A_2H_2 prolongation and atrial echo beats with a constant H_2Ae time of 40 ms until anterograde block again occurred at an A_1A_2 interval of 220 ms.

Similar results were obtained in cases 1 and 3 with the exception that anterograde block always occurred proximal to the His bundle (Fig. 1).

Reduction in the cycle length of the basic atrial pacing sequence resulted in all patients in attenuation or abolition of the anterograde gap in conduction (Table 3) because of improved final common pathway conduction or failure of slow pathway conduction.

After intravenous verapamil, slow pathway conduction at A_1A_2 intervals less than the refractory period of the fast pathway was abolished (Fig. 3). Fast pathway conduction was not affected by verapamil.

Discussion

In 1952 Lown *et al.* reported the association between a short PR interval on the resting 12-lead electrocardiogram and paroxysms of rapid heart action. This syndrome differs from the Wolff-Parkinson-White syndrome (1930) which is also characterised by a short PR interval, in that the QRS complex is narrow. It is now firmly established that at least the majority of examples of the Wolff-Parkinson-White syndrome result from an anomalous tract of tissue which bridges the annulus fibrosus and allows pre-excitation of the ventricular myocardium by this abnormal route (Durrer *et al.*, 1970). The attenuation of the PR interval in the Lown-Ganong-Levine syndrome is the result of a short AH interval (Castellanos *et al.*, 1971; Mandel *et al.*, 1971; Neuss *et al.*, 1975) and occasionally additional shortening of the HV interval (Mandel *et al.*, 1971; Both *et al.*, 1975). By analogy with the Wolff-Parkinson-White syndrome the syndrome of short PR interval and normal QRS complex might be explained by pre-excitation of the distal AV junction by a partial or complete AV nodal bypass tract as described by James (1963) or Brechenmacher (1976) (Castellanos *et al.*, 1971; James and Scherf, 1971; Mandel *et al.*, 1971). Such a tract of tissue has been histologically verified in one patient with the short PR interval, normal QRS complex syndrome (Brechenmacher *et al.*, 1974). Nevertheless, the alternative explanation of a rapidly conducting intranodal pathway (Caracta

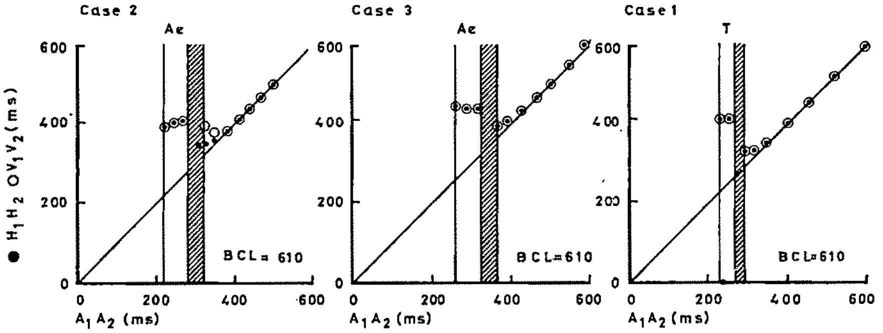

Fig. 1 *Anterograde conduction curves in case 1, 2, and 3. The hatched area is the gap zone. Atrial echo zones (Ae) or tachycardia stimulation zone (T) are indicated.*

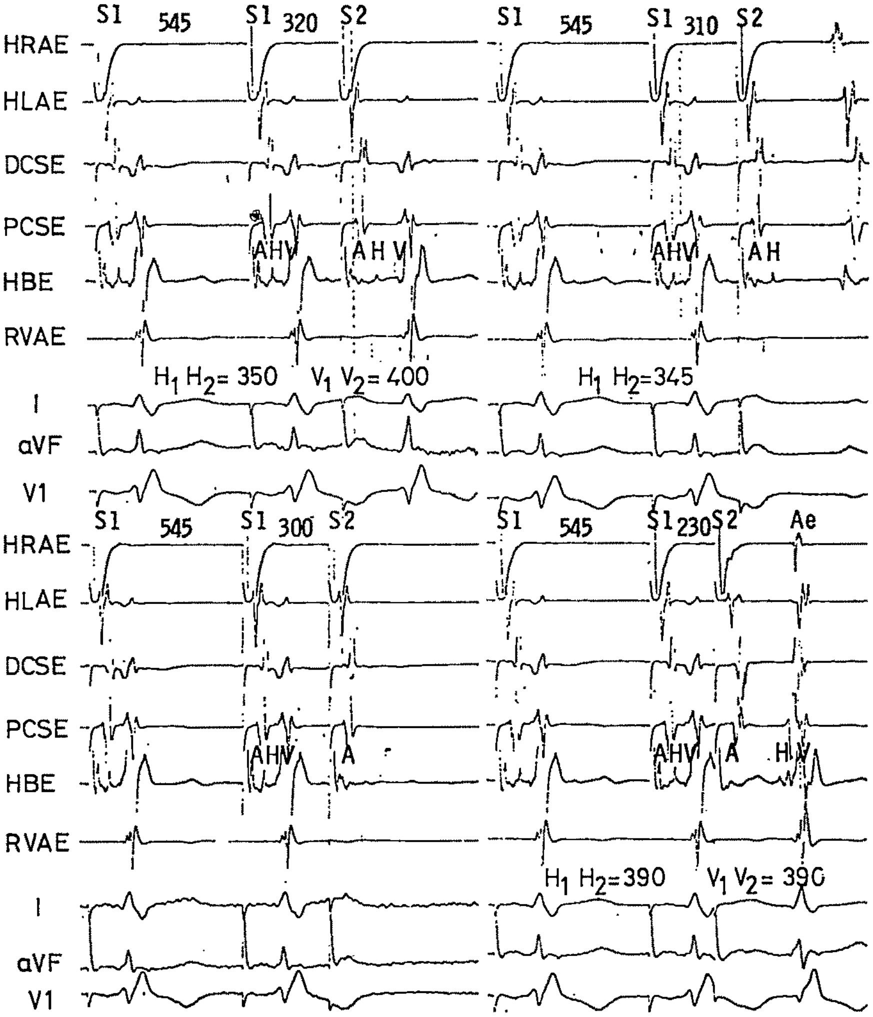

Fig. 2 *Programmed atrial premature stimuli at progressively shorter coupling intervals in case 2. HRAE, high right atrial electrogram; HLAE, high left atrial electrogram; DCSE, distal coronary sinus electrogram; PCSE, proximal coronary sinus electrogram; HBE, His bundle electrogram; RVAE, right ventricular apex electrogram; I, aVF, V1, standard surface leads.*

et al., 1973; Nowak and Neuss, 1974) is feasible in patients, similar to the cases reported here, with a normal HV time.

In our patients the minimal prolongation of the AH time in response to incremental atrial pacing (Bisset *et al.*, 1973; Neuss *et al.*, 1975), premature atrial stimulation (Castellanos *et al.*, 1971; Aranda *et al.*, 1976), and intravenous verapamil (Both *et al.*, 1975; Seipel *et al.*, 1976) is typical of the short PR interval, narrow QRS complex syndrome and more consistent with an extranodal bypass tract than an intranodal fast pathway. In the cases reported here, anatomical dissociation of the fast pathway from the AV node is very likely because conduction anterogradely through the slow AH pathway results in atrial echo beats with earliest activation on the proximal coronary sinus electrode (Narula, 1974; Agha *et al.*, 1976; Amat-y-Leon *et al.*, 1976). A concealed direct VA connection is excluded because the atrial echo beat occurs before ventricular activation.

A gap in anterograde conduction is defined as a zone within the cardiac cycle where an atrial premature beat fails to be conducted to the ventricles

Table 3 *Anterograde conduction characteristics at various basic atrial pacing rates*

Case	*Basic cycle length (ms)*	*Fast AH (AN)* pathway*		*Slow AH pathway*		*Anterograde gap* (A_1A_2)	*Atrial echo zone* (A_1A_2)
		ERP (A_1A_2)	*FRP* (H_1H_2)	*ERP* (A_1A_2)	*FRP* (H_1H_2)		
1	610	290 ms (?260)	310 ms (?260)	240 ms	400 ms	265-290 ms	245-260 ms
	430	290 ms	310 ms	—	—	—	—
2	610	305 ms (?265)	345 ms (?265)	215 ms	380 ms	270-310 ms	220-260 ms
	545	305 ms (?265)	345 ms (?265)	220 ms	390 ms	270-310 ms	225-255 ms
	500	290 ms (?240)	335 ms (?240)	220 ms	420 ms	245-285 ms	225-240 ms
	430	290 ms	325 ms	—	—	—	—
3	610	370 ms (?325)	380 ms (?325)	260 ms	415 ms	330-365 ms	265-325 ms
	375	370 ms	385 ms	—	—	—	—

*Fast AH pathway refractory periods are measured in the conventional manner from the anterograde conduction curves. AN pathway refractoriness (effective and functional) is assumed to be the A_1A_2 interval at which conduction resumes after the anterograde gap (see text).

bracketed by zones of intact conduction. The gap phenomenon was first described by Moe *et al.* (1965) in the canine heart and subsequently extended to the human heart by Durrer (1968) and Goldreyer and Bigger (1969). Durrer interpreted his findings in terms of longitudinal duality of AV nodal conduction. Early atrial premature beats, conducting rapidly down one of two AV nodal pathways, reached the distal conduction system when it was still refractory and failed to reach the ventricles. Still earlier atrial premature beats found the fast AV nodal pathway refractory and conducted slowly down the alternate pathway to reach distal tissue after it had recovered, and conduction to the ventricles, therefore, resumed. Subsequent investigations by Wit and his associates (1970a) showed that the conduction failure of early atrial systoles occurred if the functional refractory period of the AV node was less than the effective refractory period of the His-Purkinje system and that conduction resumed in response to very early atrial beats if sufficient proximal delay allowed the recovery of distal tissue. This explanation did not require the existence of proximal conduction system duality. Many examples of anterograde (Agha *et al.*, 1973; Gallagher *et al.*, 1973; Wu *et al.*, 1974) and retrograde gap (Akhtar *et al.*, 1974a, b) have now been described and classified in terms of sites of distal block and proximal delay (Damato *et al.*, 1976) and Durrer's (1968) original hypothesis still awaits confirmation.

Electrophysiological evidence of AV nodal dual conduction pathways is provided by the construction of an anterograde conduction curve (Moe *et al.*, 1956). The atrial extrastimulus technique is used to derive values of H_1H_2 for each A_1A_2 interval. A plot of H_1H_2 intervals against corresponding A_1A_2 values usually produces a smooth uninterrupted

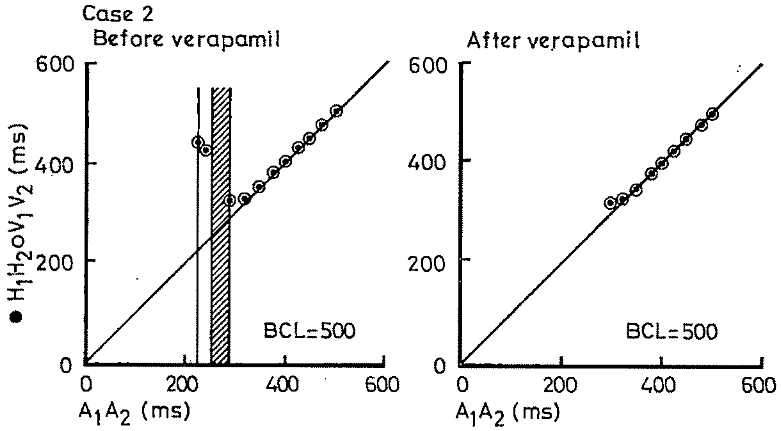

Fig. 3 *Anterograde conduction curves before and after intravenous verapamil in case 2.*

curve (Wit *et al.*, 1970b) but, where functional duality of AV nodal conduction is present, at critical A_1A_2 intervals, a sudden increase of H_1H_2 values may occur, when fast pathway conduction fails and slow pathway conduction is revealed (Denes *et al.*, 1973). Such discontinuous anterograde conduction plots were evident in 3 of the 8 patients with the short PR interval, normal QRS complex syndrome studied recently in our laboratory and reported here. Others have found similar results in this syndrome (Denes *et al.*, 1974b; Neuss *et al.*, 1975; Aranda *et al.*, 1976; Seipel *et al.*, 1976). The discontinuity of the conduction curves in the present cases is emphasised by the gap in anterograde conduction which separates slow and fast pathway conduction (Fig. 2). Conduction failure above the level of the His bundle may mask intermediate H_1H_2 intervals, but the slopes of the apparently separate curves suggests that they are truly discontinuous.

Duality of conduction at AV nodal level is further supported by the occurrence of atrial echo beats, with low to high atrial activation, at A_1A_2 intervals less than the effective refractory period of the fast pathway (Wu *et al.*, 1975).

Complete or partial bypasses of the AV node short-circuit the normal physiological delay imposed by the AV node. Failure of AH prolongation should result in AH functional refractoriness being limited by the fast pathway's effective refractory period. Bisset *et al.* (1975) found statistically shorter AH refractory periods in patients with short PR intervals. In our patients the functional refractory period of the fast pathway cannot be assessed from the shortest H_1H_2 interval achieved in response to atrial extrastimuli because it is uncertain where the fast pathway inserts into the AV nodal-His axis and because, during the gap in anterograde conduction, block occurs at a supra-Hisian level. Concealed fast pathway conduction probably continues during the anterograde gap zone because slow pathway conduction and atrial echo beats emerge simultaneously with the resumption in conduction. If the fast pathway's functional refractoriness is assumed to be the lower limit of the AH gap in conduction then conduction failure could be attributed, in part, to the short functional refractory period of the bypass. On the other hand, local geometric factors related to the abnormal insertion of the extranodal bypass into the normal AV nodel-His axis may be important (Janse, 1969).

Gap phenomena have been previously encountered in the short PR interval, normal QRS complex syndrome (Coumel *et al.*, 1972; Aranda *et al.*, 1976; Seipel *et al.*, 1976). Aranda and his colleagues found anterograde gaps in 2 of 4 cases reported and resumption of anterograde conduction was not related to refractoriness of the fast pathway. Seipel *et al.* (1976) comment that anterograde gaps are frequently seen in this condition but do not mention the mechanism involved. In one illustration from their paper (Fig. 2, p. 154) conduction resumes with additional His-Purkinje delay, despite continued rapid AH conduction. In the three examples reported here the resumption of conduction is associated with an apparently sudden increase in the AH time and the simultaneous occurrence of atrial echo beats or sustained paroxysmal tachycardia.

Although conduction of premature atrial impulses at coupling intervals to the right of the anterograde gap (Fig. 1) appears to take place through a relatively fast pathway and conduction to the left of the gap through a dissociated slower pathway, the state and extent of AV conduction during the gap cannot be known with certainty because block occurs above the level of the His bundle. In case 2 at an A_1A_2 interval of 310 ms (Fig. 2) block occurs below the level of the His bundle in the presence of continued fast pathway conduction. At shorter A_1A_2 intervals conduction block occurs proximal to the His bundle. It is probable that, throughout the gap, concealed fast pathway conduction continues to depolarise the lower AV junction at a coupling interval within the refractory period of the final common pathway to the ventricles. According to this hypothesis, slow pathway conduction is prevented by the concealed depolarisation of the lower AV junction and conduction resumes when A_2 finds the fast pathway refractory and is propagated with normal delay over the slow pathway. However, if the effective refractory period of the fast pathway is at the upper limit of the AV gap, block in this pathway may have revealed a gap in which both distal block and proximal delay were confined to the slow AH pathway. The upper limit of such a gap cannot be defined and this mechanism cannot fully account for the findings in case 2 and is unlikely in the other cases. In the examples reported here, the conduction of early atrial premature beats seems related to the shift of anterograde conduction to a slow intranodal pathway (Fig. 4) reminiscent of Durrer's (1968) original hypothesis.

Anterograde conduction characteristics assessed by the atrial extrastimulus method at higher atrial driving rates resulted in attenuation and abolition of the anterograde gap. The reduction in the gap zone resulted from improved final common pathway conduction as evidenced by the reduction of the upper limit of the gap. Abolition of the gap phenomenon resulted from failure of slow pathway conduction presumably because of increased AV nodal refractoriness at higher pacing rates (Denes *et al.*, 1974a).

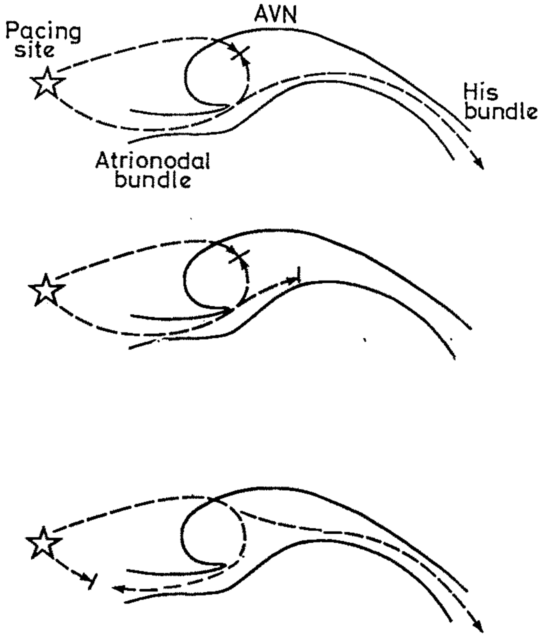

Fig. 4 *Diagrammatic representation of the mechanism of gap production.* Upper panel: *conduction at intervals to the right of the gap;* centre panel: *block in AV transmission producing a gap in the anterograde conduction curve;* lower panel: *resumption of conduction at intervals to the left of the gap.*

Verapamil does not affect atrial or anomalous bypass tract conduction characteristics, but selectively lengthens both refractoriness and conduction time of the AV node (Spurrell *et al.*, 1974; Zipes and Fischer, 1974). In all 3 patients verapamil prevented slow pathway conduction at A_1A_2 values less than the refractory period of the fast pathway thus preventing the resumption of conduction at close atrial coupling intervals and abolishing the gap phenomenon.

Anterograde gap phenomena produced by block distal to the AV node are generally masked by fast basic pacing rates and by drugs such as beta-blockers (Wit *et al.*, 1970a; Akhtar *et al.*, 1974a) and verapamil which increase AV nodal functional refractoriness. These manoeuvres cannot, therefore, be used to distinguish gap phenomena related to AV nodal duality from those produced by inhomogeneous refractoriness along the length of a single AV nodal-His Purkinje pathway.

It is seemingly paradoxical that improved conduction responsible for the short PR interval, normal QRS complex syndrome should lead to failure of conduction. Partial or complete AV nodal bypasses produce early and abnormal activation of distal junctional tissue and add another dimension to longitudinal inhomogeneity of atrioventricular transmission responsible for the high incidence of anterograde gaps in this syndrome.

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Re-entrant tachycardia using two bypass tracts and excluding AV node in short PR interval, normal QRS syndrome

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SUMMARY In patients with the short PR interval, normal QRS complex syndrome, paroxysmal tachycardias are usually the result of circus movement involving the AV node and a partial or complete AV nodal bypass. We report 2 patients with this syndrome who suffered distressing rapid paroxysms of tachycardia but in whom there was evidence of a concealed direct VA connection. In both patients, tachycardia was initiated with critical AV prolongation distal to the His bundle, in response to programmed atrial premature stimuli. The constancy of the timing of the atrial echo from the onset of the QRS complex in the presence of a varying HV interval is evidence for involvement of the ventricles in the re-entry pathway. In addition, in both patients the appearance of left bundle-branch block during tachycardia was associated with appropriate prolongation of tachycardia cycle length consistent with the presence of a direct VA connection. The short AH interval during tachycardia and the absence of critical AH prolongation suggests the participation of a rapidly conducting pathway in the anterograde limb of the tachycardia circuit.

The syndrome of short PR interval and normal QRS complex associated with paroxysmal rapid heart action was described by Lown *et al.* (1952). The advent of techniques of intracardiac recording and stimulation has allowed analysis of the syndrome in great detail. It is now generally accepted that the short PR interval is the result of conduction in a partial or complete AV nodal bypass (Durrer *et al.*, 1970; Castellanos *et al.*, 1971; Mandel *et al.*, 1971). Intracardiac recordings in patients with this syndrome show a short AH interval as a result of conduction in the accessory pathway. Alternative explanations of the short PR interval include enhanced AV nodal conduction and have been enumerated by Caracta *et al.* (1973). The mechanism of tachycardia in the short PR interval, normal QRS complex syndrome has not been clearly elucidated. Intracardiac electrophysiological studies (Mandel *et al.*, 1971; Denes *et al.*, 1974) suggest that the most common mechanism is associated with block in the rapidly conducting pathway and critical prolongation of the AH interval allowing re-entry towards the atrium in the fast extranodal pathway. In the 2 patients described in this report a different mechanism was evident.

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Patients and methods

A 63-year-old man (case 1) was admitted to hospital in March 1977 for investigation of paroxysmal palpitation which he had experienced for 12 years. Acute attacks had failed to respond reliably to intravenous propranolol or verapamil and in recent months he had required DC conversion to restore sinus rhythm. Oral therapy which had included propranolol and disopyramide reduced the frequency of attacks. Physical examination and routine investigations were normal. The surface electrocardiogram showed a PR interval of 0·11 s during sinus rhythm and a normal QRS complex.

The second patient (case 2), a 26-year-old man suffered rapid paroxysms of palpitation since the age of 12 years. Various medications including digoxin, procainamide, propranolol, and verapamil had failed to control attacks. In the 2 years before investigation he had had several attacks requiring DC conversion to sinus rhythm. On other occasions intravenous verapamil was administered and successfully terminated the tachycardia only once. The patient was admitted for investigation in June 1977. Physical examination and routine investigations were normal. The surface electrocardiogram revealed a PR interval of 0·12 s and normal QRS complexes.

Both patients were studied in the postabsorptive non-sedated state. All medications were stopped 4 days before study. Four pacing electrodes were introduced into the right femoral vein under local anaesthetic and were positioned fluoroscopically in the apex of the right ventricle, against the septal leaflet of the tricuspid valve and in the high right atrium. In case 1 an additional electrode catheter was introduced via the left basilic vein and positioned in the coronary sinus. All intracardiac signals were filtered between 50 and 700 Hz and recorded simultaneously with surface leads I, aVF, and V1 on an Elema Mingograph at 100 mm/s, with time markings at 1-second intervals.

Stimulation was performed using a Devices 4270 isolated stimulator with 1·5 ms square wave pulses delivered at approximately twice the diastolic threshold.

DEFINITIONS

The following abbrevations, terms, and definitions are used throughout the text—

A_1, H_1, V_1	the atrial, His bundle, and ventricular electrogram during basic atrial pacing.
A_2, H_2, V_2	the atrial, His bundle, and ventricular electrograms produced by premature atrial stimulation.
AH	the interval between the intrinsic deflection of the atrial electrogram and the intrinsic deflection of the His bundle electrogram on the His bundle electrode.
HV	the interval between the intrinsic deflection of the His bundle electrogram and the earliest ventricular activation in any lead.
VA′	the interval between the earliest ventricular activation in any lead and the retrograde atrial electrogram in the high right atrial electrode.

Results

CASE 1

At electrophysiological study during sinus rhythm the AH interval was 60 ms with an HV interval of 35 ms. During incremental atrial pacing the AH interval increased from 60 ms at a cycle length of 610 ms to 80 ms at a cycle length of 375 ms. Programmed atrial premature stimuli were delivered throughout electrical diastole. Fig. 1a shows the anterograde conduction curve constructed by plotting the H_1H_2 and V_1V_2 intervals against the coupling interval of the premature stimulus, A_1A_2. A_1A_2 values between 610 and 385 ms produced a small prolongation of the H_1H_2 interval. As the coupling interval was shortened from 385 ms to 310 ms prolongation of the H_2V_2 interval occurred and left bundle-branch block appeared. Within this range of coupling intervals the A_2H_2 interval increased by only 10 ms to 90 ms.

Fig. 2a shows initiation of tachycardia at a coupling interval of 310 ms. The H_2V_2 interval increased to 85 ms at this coupling interval. At all

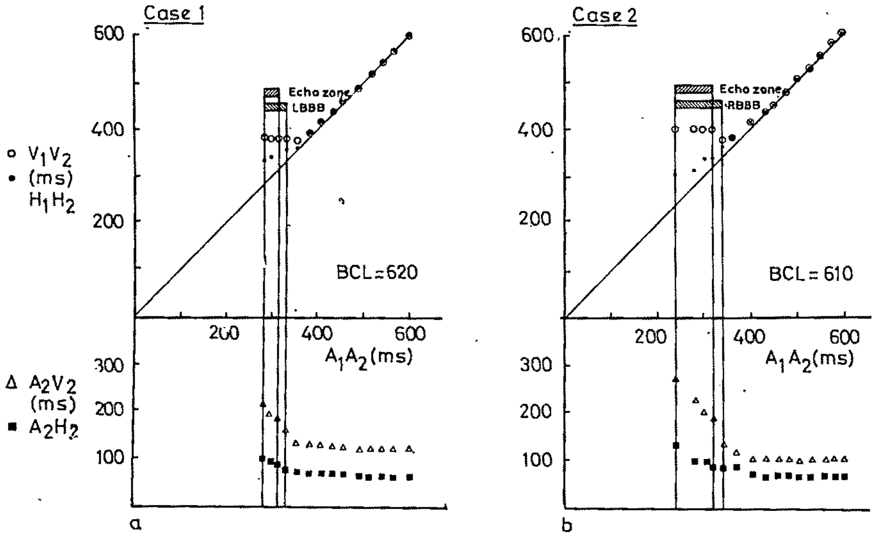

Fig. 1 *Anterograde conduction curves in cases 1 and 2.*

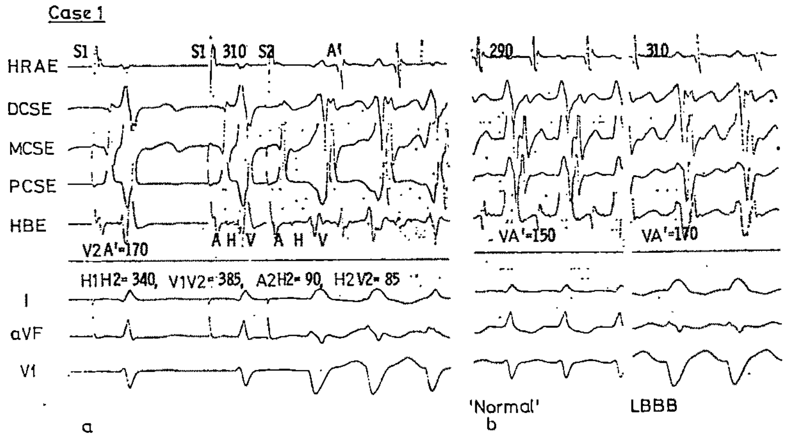

Fig. 2 (*a*) *Initiation of tachycardia by premature atrial stimulation* (S_2).
(*b*) *Tachycardia with normal QRS complexes and a cycle length of 290 ms compared with tachycardia with left bundle-branch block and cycle length of 310 ms.*
HRAE, high right atrial electrogram; DCSE, distal coronary sinus electrogram; MCSE, mid-coronary sinus electrogram; PCSE, proximal coronary sinus electrogram; HBE, His bundle electrogram; I, aVF, V1, surface electrocardiographic leads.

intervals of A_1A_2 which resulted in left bundle-branch block and an atrial echo or sustained tachycardia the V_2A' interval remained between 165 and 170 ms despite variations in the A_2H_2 and H_2V_2 intervals. The same V_2A' interval was observed during tachycardia. Narrow complex tachycardia was not initiated by a single atrial premature stimulus. During tachycardia earliest activation of the atria occurred on the proximal coronary sinus electrogram. A single ventricular stimulus during tachycardia 15 ms before the onset of the His bundle potential was conducted retrogradely, resetting the atrial electrogram without disturbing the His bundle depolarisation or altering the atrial activation sequence. This is shown in Fig. 3. Appropriately timed ventricular stimuli during tachycardia resulted in conversion of the left bundle-branch block tachycardia to narrow complex tachycardia. When this occurred the cycle length of tachycardia was shortened by an amount corresponding to the shortening of the VA' interval (Fig. 2b). Fig. 4a shows narrow complex tachycardia with a short A'H interval of 55 ms and normal HV interval. Termination of both narrow and broad complex tachycardia was reliably achieved by rapid atrial pacing or double ventricular stimuli. Programmed ventricular premature stimuli after a regular pacing sequence resulted in constancy of retrograde conduction time with earliest activation of the atria on the proximal coronary sinus electrogram.

CASE 2

During sinus rhythm the AH interval was 65 ms and HV 35 ms. Incremental atrial pacing prolonged the AH interval from 65 ms at a cycle length of 610 ms to 90 ms at a paced cycle length of 375 ms. The HV interval remained unchanged. The H_1H_2 and V_1V_2 intervals resulting from progressively shortened A_1A_2 values are shown in Fig. 1b.

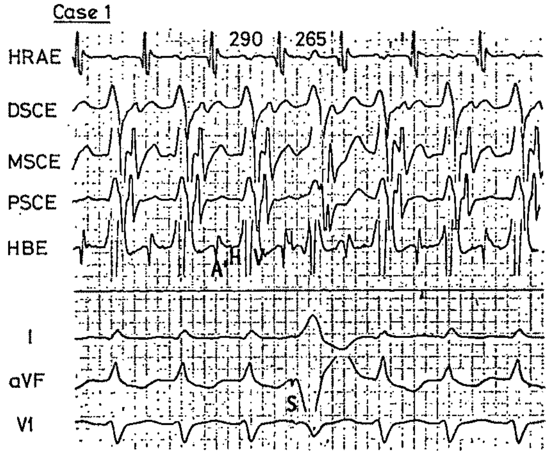

Fig. 3 *Premature ventricular stimulation during tachycardia resulting in exact atrial capture. S, stimulus artefact.*

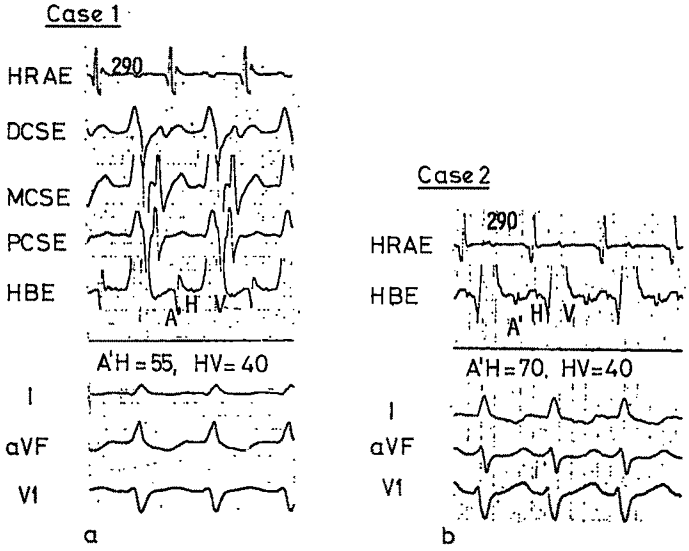

Fig. 4 *Tachycardia in case 1 (a) and case 2 (b) demonstrating short AH interval.*

Values of A_1A_2 between 610 and 360 ms caused minimal prolongation of the A_2H_2 intervals. Earlier premature stimuli resulted in gradual prolongation of the H_2V_2 interval. Fig. 5 compares a premature stimulus at 440 ms with a stimulus at 320 ms which resulted in prolongation of the H_2V_2 interval to 105 ms, right bundle-branch block, and initiation of tachycardia. Shorter coupling intervals resulted in similar responses. At all coupling intervals which produced atrial echo beats or sustained tachycardia the V_2A' interval remained constant at 210 to 215 ms, though the H_2V_2 interval varied from 105 to 135 ms and the A_2H_2 interval varied minimally.

Appropriately timed single ventricular stimuli during right bundle-branch block tachycardia resulted in conversion to narrow complex tachycardia without change in cycle length. On one occasion tachycardia with left bundle-branch block was precipitated by a non-programmed stimulus. The VA′ interval increased by 30 ms with a corresponding increase in cycle length. Fig. 6 shows all 3 varieties of tachycardia. Right bundle-branch block and normal complex tachycardia both had a cycle length of 290 ms with VA′ intervals of 210 ms, whereas left bundle-branch block tachycardia had a cycle length of 320 ms and VA′ of 240 ms. Exact capture of the atria by ventricular stimulation could not be achieved presumably because right ventricular apical stimuli were too remote from the tachycardia circuit. Fig. 4b shows a short A′H interval of 70 ms and HV of 40 ms during narrow complex tachycardia. Termination of tachycardia was reliably achieved by rapid atrial pacing or appropriately timed double ventricular stimuli. Programmed ventricular premature stimuli resulted in constancy of retrograde conduction time.

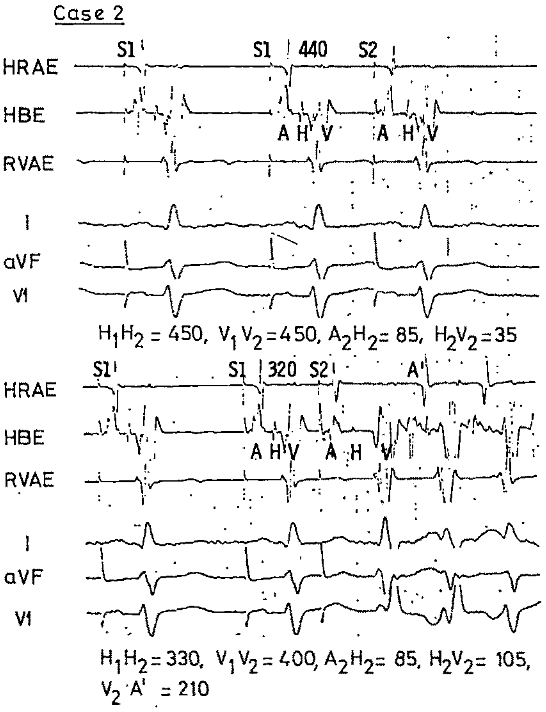
Case 2
S1
S1
440
S2
HRAE
HBE
A H' V
A H' V
RVAE
I
aVF
V1
H_1H_2 = 450, V_1V_2=450, A_2H_2= 85, H_2V_2=35
S1
S1
320
S2
A'
HRAE
HBE
A H V
A H V
RVAE
I
aVF
V1
H_1H_2=330, V_1V_2= 400, A_2H_2= 85, H_2V_2= 105, V_2A' = 210

Fig. 5 *Atrial premature stimuli (S_2) in case 2 at coupling intervals of 440 ms (upper panel) and 320 ms (lower panel). RVAE, right ventricular apical electrogram.*

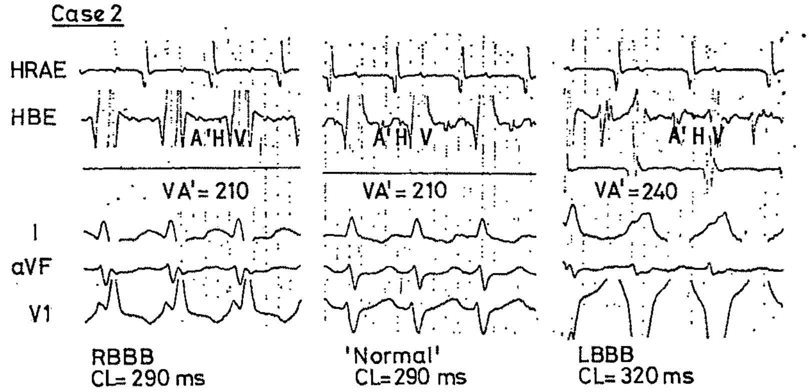

Fig. 6 *Three forms of tachycardia in case 2.*

Discussion

The presence of a short PR interval and narrow QRS complex on the surface electrocardiogram is frequently associated with paroxysmal tachycardias (Lown *et al.*, 1952; Castellanos *et al.*, 1971). In recent years electrophysiological studies have shown abnormal responses to atrial pacing in many of these patients. In normal subjects, incremental atrial pacing or programmed atrial premature stimuli at progressively shorter coupling intervals results in smooth prolongation of AH conduction (Wit *et al.*, 1970). In patients with the short PR interval, normal QRS complex syndrome this prolongation of the AH interval may be attenuated or absent (Castellanos *et al.*, 1971; Bisset *et al.*, 1973; Caracta *et al.*, 1973; Denes *et al.*, 1974; Neuss *et al.*, 1975a).

This response has been attributed to complete or partial bypass of the AV node by accessory tracts (James, 1961) inserting into the lower AV junction. The existence of a bypass tract has been proven histologically in one patient with this syndrome (Brechenmacher *et al.*, 1974).

In both patients described here the AH interval increased minimally in response to incremental atrial pacing and programmed atrial premature stimuli, suggesting that conduction to the ventricles was not occurring in the normal delaying pathways. Conduction in a 'fast pathway' with short functional refractoriness such as an atrionodal bypass, at earlier coupling intervals of atrial premature stimuli results in preactivation of the AV junction. The short AH functional refractoriness (Bisset *et al.*, 1975) may result in prolongation of the H_2V_2 interval and bundle-branch block at early coupling intervals (Coumel *et al.*, 1972; Seipel *et al.*, 1976). Fig. 7 is a diagrammatic representation of this mechanism.

Dual intranodal pathways have been demonstrated in animals and in patients with intra-AV nodal re-entry (Moe and Mendez, 1966; Goldreyer and Damato, 1971; Denes *et al.*, 1973). A similar phenomenon may be seen in patients with the short PR interval, normal QRS complex syndrome and is thought to represent block in the fast intranodal or extranodal pathway (Denes *et al.*, 1974). In patients with duality of intranodal conduction onset of tachycardia during programmed atrial stimulation is associated with critical AH delay. In the patients described here, no sudden prolongation of the AH interval occurred and the major delay occurred distal to the site of His bundle recording. These observations suggest continued anterograde conduction in the fast pathway and the lack of effect of verapamil on tachycardia cycle length and AH interval, lends credence to this hypothesis. With critical AV conduction delay atrial echo beats or sustained tachycardia is initiated with return to the atria either via the AV node or a concealed direct VA connection.

The participation of a concealed direct VA connection (Spurrell *et al.*, 1974a; Tonkin *et al.*, 1975)

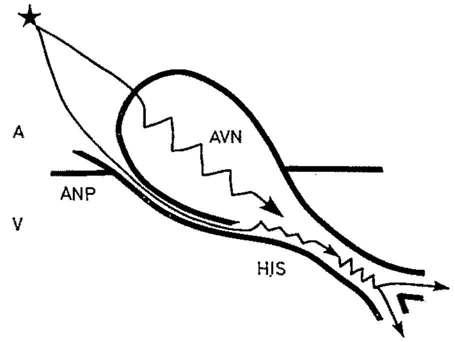

Fig. 7 *Diagram of mechanism of AV junctional pre-excitation by atrial premature stimulus (star). AVN, atrioventricular node; ANP, atrionodal pathway; His, His bundle; A, atrium; V, ventricles.*

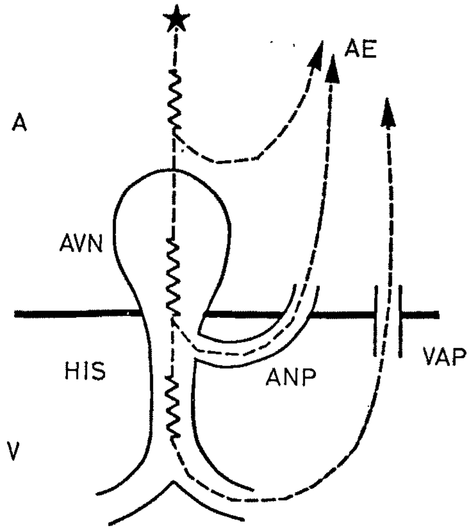

Fig. 8 *An atrial premature stimulus (star) may result in anterograde conduction delay sufficient to allow re-entry to the atrium (AE). Such re-entry may involve an atrionodal pathway (ANP) or a direct ventriculoatrial pathway (VAP). Critical conduction delay above the His bundle associated with a constant H-AE interval suggests re-entry within the AV node or via an atrionodal pathway. Delay below the site of the His bundle with a constant V-AE interval suggests re-entry via a direct VA pathway.*

in the tachycardia circuit is suggested by the timing of the atrial echo beat. The constancy of the V_2A' interval in the presence of a varying H_2V_2 interval makes it unlikely that the re-entrant pathway is located entirely above the His bundle and implies the participation of the ventricles in the tachycardia circuit. Intra-AV nodal re-entry or re-entry in an atrionodal pathway results in nearly constant H_2A' intervals. If, however, the H_2V_2 is constant no conclusion can be drawn about the site of re-entry. Fig. 8 summarises these concepts.

The appearance of atrial echoes with critical HV conduction delay has been described previously (Lozano *et al.*, 1973; Varghese *et al.*, 1974; Neuss *et al.*, 1975b). Both Lozano *et al.* (1973) and Varghese *et al.* (1974) interpreted their findings as indicative of a combination of intraventricular and intra AV nodal re-entry. However, a concealed, direct, VA connection could not be excluded in their patients. The short AH in response to programmed atrial premature beats and the lack of AH prolongation with increasing prematurity of atrial stimulation suggests the presence of a fast anterograde pathway in the patient reported by Lozano *et al.* (1973). Neuss *et al.* (1975b) report a patient with similar findings to the patients described here. They also observed constancy of the V_2A' interval in the presence of an increasing H_2V_2 interval in response to premature atrial stimuli delivered during sinus rhythm. This observation was regarded as proof of involvement of the ventricles within the re-entrant circuit. No comment was made concerning the mechanism of critical conduction delay. The absence of atrial echo beats or tachycardia at later coupling intervals of A_2 is probably related to limiting atrial refractoriness at the time of retrograde activation of the VA pathway (Pritchett *et al.*, 1977), or alternatively to concealed anterograde invasion of the VA pathway during atrial stimulation (Zipes *et al.*, 1974).

Additional evidence for an accessory concealed VA connection in our patients was provided by the following observations.

(1) In both patients the appearance of left bundle-branch block during tachycardias was associated with an increase in VA′ conduction and tachycardia cycle length (Coumel and Attuel, 1974; Pritchett *et al.*, 1976; Spurrell *et al.*, 1974b).

(2) In case 1 coronary sinus recordings revealed early activation of the low left atrium near the proximal coronary sinus during tachycardia. This does not prove that retrograde activation is via a direct AV pathway since retrograde conduction in an atrionodal pathway may produce similar eccentric atrial activation. However, a ventricular premature stimulus, delivered 15 ms before the His bundle potential, conducted retrogradely with exact atrial capture and identical atrial activation sequence. Retrograde conduction in an atrionodal pathway would be impossible in these conditions and the retrograde limb of the re-entrant circuit, is therefore, a direct VA pathway (Sellers *et al.*, 1976).

The coexistence of anomalous atrionodal and atrioventricular pathways has been described previously (Coumel *et al.*, 1971, 1972; Neuss *et al.*, 1975b; Zipes *et al.*, 1974; Castellanos *et al.*, 1975) and unusual re-entry mechanisms may result from these combinations. The mechanism of re-entry in our patients is dependent on an interaction between two functionally abnormal pathways. Conduction delay at infra-Hisian level occurs as a result of pre-activation of the AV junction and retrograde conduction occurs when critical delay is sufficient to allow re-entry in the VA pathway and atrial myocardium.

In the patients described by Lozano and his colleagues (1973) tachycardia was initiated in the presence of a short AH interval which persisted during sustained tachycardia. These observations suggest the incorporation of a partial or complete AV nodal bypass tract in the anterograde limb of the re-entrant circuit. Re-entrant circuits utilising an anterograde fast pathway bypassing the AV node and a retrograde direct VA pathway may result in rapid, distressing tachycardias unresponsive to therapy directed towards the AV node itself, and in these cases verapamil was not effective. Detailed electrophysiological studies are required to define the tachycardia mechanism in these patients.

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Congestive heart failure in normotensive man

Haemodynamics, renin, and angiotensin II blockade

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SUMMARY The role of the renin angiotensin system was evaluated in 18 normotensive patients with chronic congestive heart failure and in 5 controls. No correlation was observed between plasma renin activity and cardiac index. There was a significant inverse correlation between renin and pulmonary capillary wedge pressure ($r = -0{\cdot}61, P < 0{\cdot}01$). Renin values of the patients appeared to be increased when compared with controls with similar left ventricular filling pressure. Specific angiotensin II inhibition by saralasin decreased arterial pressure in 8 out of 14 patients: their renin was significantly higher than that of the remaining 6 patients ($P < 0{\cdot}01$). The 2 patients with the lowest renin levels responded to saralasin with a blood pressure increase. Left ventricular filling pressure decreased in all but these latter 2 patients with either little change or an increase in stroke volume. Thus, renin levels appear to be increased in normotensive patients with congestive heart failure when related to left ventricular filling pressure. Renin via angiotensin II plays a role in the blood pressure control of many patients with congestive heart failure. In some patients angiotensin II blockade appears to improve cardiac function by unloading the left ventricle.

Renin via angiotensin II plays an important role in blood pressure homeostasis (Sancho *et al.*, 1976; Posternak *et al.*, 1977) and in sustaining blood pressure in various forms of hypertensive diseases (Brunner *et al.*, 1974a; Streeten *et al.*, 1976). Not only does angiotensin regulate the circulation by modifying arteriolar tone, but also renal haemodynamics have been shown to modulate its generation (Davis and Freeman, 1976). Thus, the renin-angiotensin system represents an important link in the chain of mechanisms regulating the circulation.

What role does the renin-angiotensin system play in congestive heart failure? Recent studies in animals have shown that renin secretion is high in the early stages of acute experimental congestive heart failure (Watkins *et al.*, 1976; Morris *et al.*, 1977) and may later return to normal after compensatory salt and water retention (Watkins *et al.*, 1976). These studies suggest that the renin-angiotensin system participates in the genesis of experimentally-induced heart failure. In patients with chronic congestive heart failure, renin levels have been found to be high, normal, or low (Brown *et al.*, 1970; Nicholls *et al.*, 1974). So far as is known there are no clinical studies available relating plasma renin activity to haemodynamic indices of cardiac function in normotensive patients with congestive heart failure. In addition, the haemodynamic effects of specific inhibition of angiotensin in such patients have not yet been reported.

The present study was designed to determine relations between plasma renin activity and various haemodynamic indices in normotensive patients with congestive heart failure. In addition, the effects of specific angiotensin inhibition by saralasin (Pals *et al.*, 1971) were assessed. Our results suggest that plasma renin activity is related to left ventricular filling pressure and that specific inhibition of the renin-angiotensin system can improve cardiac function in many patients.

Subjects and methods

Fourteen men and nine women undergoing elective diagnostic cardiac catheterisation were included in the study. Ages ranged from 21 to 70 years. Five patients with chest pain but no clinical evidence of congestive heart failure were labelled controls. The other 18 had clinical evidence of congestive heart failure of at least one year's duration. The severity of heart failure was graded as follows: class II patient comfortable at rest, ordinary activity result-

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ing in dyspnoea; class III less than ordinary activity causing dyspnoea; class IV inability to carry on any physical activity without dyspnoea (New York Heart Association, Criteria Committee, 1964). The evaluation of each patient included left ventriculography and coronary arteriography.

The study was approved by the Hospital Ethics Committee. Informed consent was obtained from each patient after the nature and purpose of the study were explained.

All patients were admitted to the cardiology division. They received a constant dietary regimen containing 3 to 5 g NaCl per day for at least 3 days before the study. After 12 hours overnight fast, they were brought to the catheterisation laboratory. On the morning of the study, no premedication was given but the patient's usual oral digitalis preparation was administered. A Swan-Ganz flow-directed balloon-tipped catheter was introduced through an antecubital vein. A short polyethylene catheter (Seldicath) was placed percutaneously into a radial artery for the continuous monitoring of arterial pressure and arterial blood sampling.

After the placement of the catheters the patients were allowed to rest for 45 minutes. At that time, control haemodynamic measurements were obtained. Saralasin was then administered intravenously by a constant infusion pump (Sage Mod. 355). The initial rate of infusion was 1 μg/kg per min. This was subsequently increased stepwise to a maximum of 10 μg/kg per min or until mean arterial blood pressure fell by 20 mmHg. This maximal dose was chosen to assure complete blockade of angiotensin. After 45 minutes at the maximal infusion rate, all measurements were repeated.

Pressures were monitored using Statham transducers (P23Dd) and inscribed on a Hewlett Packard 14560 recorder. Mean pulmonary capillary wedge pressure was used as an index of left ventricular end-diastolic pressure.

Cardiac output was assessed by the direct Fick method. Oxygen consumption was measured with a Fleisch Metabograph (Metabo-Epalinges) (Fleisch, 1954). During the middle period of the timed respiratory collection, duplicate blood samples of 2 ml were drawn from the pulmonary and radial arteries into heparinised syringes. Blood oxygen saturation was determined on a co-oximeter (IL 182 Instrumentation Lab. Inc.). For the measurements of plasma renin activity, 7 ml blood were drawn in chilled tubes containing EDTA. We handled plasma at 4 °C because we have been unable to confirm the observation that chilling of the blood before separation can lead to a variable but often considerable rise in plasma renin activity (Sealey *et al.*, 1977). After centrifugation the plasma was immediately frozen and stored at −28 °C. Renin activity was quantified by radioimmunoassay of angiotensin I generated during incubation under standard conditions (Sealey *et al.*, 1972).

CALCULATIONS

Mean pressures were obtained from electronically integrated records. The systemic vascular resistance (SVR) in dyne s^{-1} cm^{-5} was calculated from the formula $\frac{MAP - RA}{CO} \times 80$, where MAP = mean arterial pressure; RA = mean right atrial pressure; CO = cardiac output; and 80 is the factor for converting resistance units to dyne s^{-1} cm^{-5}.

Mean and standard error of the mean were calculated and the data were compared by Student's paired and unpaired t test. Correlation coefficients were obtained for plasma renin activity and the various haemodynamic measurements. In all cases, P values of less than 0·05 were considered significant.

Results

CLINICAL CHARACTERISTICS

The clinical data of the 23 subjects are summarised in Table 1. Three of the 5 controls without congestive heart failure were found to have coronary artery disease and 2 had no evidence of disease. The diagnoses of the 18 patients with congestive heart failure included mitral and aortic valvular disease, coronary artery disease, and cardiomyopathy. According to the New York Heart Association criteria for congestive heart failure, one patient was class IV, 11 were class III, and 6 were class II. All but 3 of the patients with congestive heart failure were receiving a digitalis preparation and 11 had, in addition, diuretic therapy; in 2 frusemide was stopped 5 and 3 days before study (cases 16 and 17). Plasma sodium and potassium concentrations were similar whether the patients were on diuretic therapy or not.

INITIAL HAEMODYNAMIC AND RENIN MEASUREMENTS

Individual haemodynamic and plasma renin data are shown in Table 2. Resting mean arterial pressure averaged 91 ± 3·5 mmHg (mean ± SEM), for the 18 patients with congestive heart failure and 99 ± 4·3 mmHg for the 5 controls. Mean right atrial pressure for the two groups was identical, 3·6 ± 0·6 mmHg, while mean pulmonary arterial pressure was 28 ± 3·2 and 12·8 ± 0·6 mmHg, respectively ($P < 0{\cdot}025$). In the group with heart failure, mean pulmonary capillary wedge pressure was 19 ±

Table 1 *Clinical and biochemical characteristics*

Case no.	*Age (yr)*	*Sex*	*Diagnosis*	*CHF class*	*Digitalis (mg/day)*	*Diuretic (mg/day)*	*Serum electrolytes mmol/l*	
							Na	*K*
1	63	M	Coronary artery disease	—	—	—	142	3·8
2	63	F	Chest pain	—	—	—	143	3·5
3	56	F	Chest pain	—	—	—	139	3·7
4	54	M	Coronary artery disease	—	—	—	141	4·3
5	67	F	Coronary artery disease	—	—	—	140	4·2
6	59	M	Aortic regurgitation	III	Digoxin 0·25	Frusemide 40 Spironolactone 50	136	4·1
7	70	M	Mitral regurgitation	IV	Digoxin 0·25	Frusemide 40 Spironolactone 100	143	4·3
8	60	M	Coronary artery disease	II	—	Frusemide 40 Spironolactone 75	141	4·0
9	57	F	Aortic regurgitation and stenosis	II	—	—	142	4·0
10	58	M	Aortic regurgitation and stenosis	III	Digoxin 0·25	Frusemide 40 Spironolactone 25	140	4·1
11	50	M	Coronary artery disease	III	Digoxin 0·25	—	139	4·1
12	50	M	Cardiomyopathy	III	Digoxin 0·25	Hydrochlorothiazide 50 Amiloride 5	140	4·0
13	53	M	Aortic regurgitation and stenosis; coronary artery disease	II	Digoxin 0·25	Hydrochlorothiazide 50 Amiloride 5	142	3·9
14	63	F	Mitral regurgitation	III	Digoxin 0·25	Spironolactone 75 Frusemide 40	140	3·7
15	21	M	Aortic regurgitation	II	—	—	139	4·0
16	70	M	Aortic stenosis	III	Digoxin 0·25	Frusemide 40 Chlorthalidone 100	133	4·2
17	64	F	Mitral regurgitation	III	Digoxin 0·50	Frusemide 80/week	142	4·1
18	55	M	Mitral regurgitation	II	Digoxin 0·25	—	141	4·0
19	58	F	Mitral regurgitation	III	Digitoxin 0·3	Chlorthalidone 100	143	4·0
20	70	F	Aortic regurgitation	II	Digoxin 0·25	—	141	4·4
21	61	F	Mitral regurgitation and stenosis	III	Digoxin 0·25	—	144	4·2
22	51	M	Mitral stenosis	III	Digoxin 0·5	Hydrochlorothiazide 50 Amiloride 5	140	3·6
23	65	M	Mitral regurgitation	III	Digoxin 0·25	—	139	4·7

Table 2 *Haemodynamic and renin data before and during saralasin infusion*

Case no.	*Mean arterial pressure (mmHg)*		*Mean right atrial pressure (mmHg)*		*Mean pulmonary artery pressure (mmHg)*		*Mean pulmonary capillary wedge pressure (mmHg)*		*Heart rate (beats/min)*		*Cardiac index (l/min per m^2)*		*Stroke volume index (ml/syst per m^2)*		*Systemic vascular resistance (dyne s^{-1} cm^{-5})*		*Plasma renin activity (ng/ml per hr)*	
	C	*S*	*C*	*S*	*C*	*S*	*C*	*S*	*C*	*S*	*C*	*S*	*C*	*S*	*C*	*S*	*C*	*S*
1	85	90	5	4	13	12	7	7	75	75	2·9	2·5	38	33	1140	1419	2·0	1·6
2	95	98	3	3	14	14	6	5	73	77	2·5	2·6	34	33	1636	1617	3·2	1·6
3	110	110	5	5	14	15	8	8	68	75	2·7	2·3	40	30	1615	1909	2·7	2·4
4	105	100	3	1	12	9	6	4	75	75	4·0	3·3	53	44	1118	1320	3·7	3·5
5	98	—	2	—	11	—	5	—	72	—	3·3	—	46	—	1182	—	1·3	—
6	70	62	−2	−2	10	9	5	2	52	55	1·6	2·2	31	41	2074	1305	9·4	32
7	130	110	4	5	50	55	37	24	83	85	2·0	2·0	25	24	3064	2625	1·9	2·2
8	120	110	4	3	28	21	17	12	110	94	3·5	2·9	32	30	1428	1630	9·0	19
9	92	70	−2	−3	12	7	6	3	75	75	2·9	4·4	38	59	1478	732	14	46
10	77	70	6	8	47	41	27	25	90	82	3·1	2·8	34	35	1183	1127	8·1	40
11	92	72	2	2	18	12	12	6	77	84	3·3	3·7	43	45	1270	862	5·6	6·7
12	90	87	2	0	31	21	23	15	58	50	3·2	2·6	56	52	1235	1513	3·3	9·5
13	91	87	0	−2	12	8	8	3	82	80	2·9	2·8	36	35	1348	1392	13	40
14	80	<50	−2	—	11	—	5	—	90	—	2·1	—	23	—	2060	—	5·8	—
15	97	97	4	0	18	14	14	9	63	75	2·8	3·7	45	50	1550	1232	2·3	2·1
16	80	79	2	2	42	37	25	22	60	50	2·1	1·9	35	38	1570	1722	4·6	12·5
17	87	87	6	2	48	47	29	17	85	90	1·3	1·9	15	21	3411	2429	1·5	2·3
18	80	85	3	1	39	35	26	20	75	77	2·7	2·5	36	32	1081	1258	1·8	1·5
19	83	98	6	7	23	25	16	20	80	85	2·0	2·0	25	24	1785	2141	1·2	1·1
20	105	155	8	—	28	—	23	40	65	60	2·4	—	37	—	2156	—	0·53	0·67
21	93	—	1	—	34	—	27	—	75	—	4·2	—	56	—	1168	—	2·3	—
22	85	—	4	—	34	—	23	—	90	—	3·1	—	34	—	1117	—	2·4	—
23	85	—	6	—	20	—	14	—	70	—	3·4	—	49	—	1170	—	2·2	—

C, Control; S, During saralasin infusion.

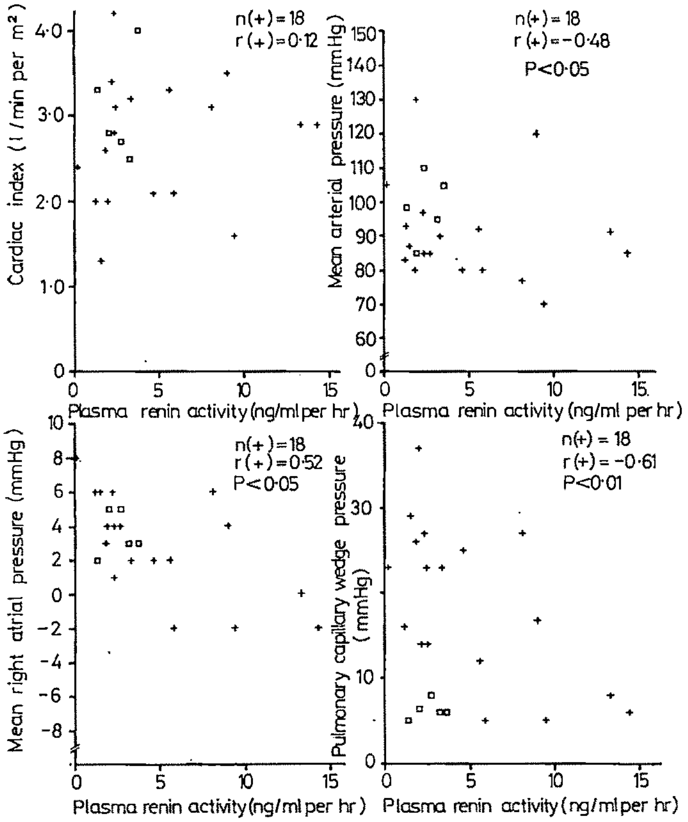

Fig. 1 *Relation between plasma renin activity and cardiac index, mean arterial pressure, mean right atrial pressure, and pulmonary capillary wedge pressure. Controls* (☐) *and patients with congestive heart failure* (+). *Correlations are calculated only for the heart failure patients. Cardiac index did not correlate with renin values. The most significant correlation was observed between plasma renin activity and pulmonary capillary wedge pressures.*

2·2 mmHg as compared with 6·4 ± 0·5 mmHg ($P < 0{\cdot}01$) in the controls. Average heart rate at rest was nearly the same in the two groups, being 77 ± 3·3 and 73 ± 1·3 beats per min, as were the mean cardiac indexes of 2·7 ± 0·2 and 3·1 ± 0·3 l/min per m^2, respectively. The stroke volume index of 36 ± 2·6 in the patients with heart failure was slightly less than 42 ± 3·3 ml/syst per m^2 in the controls. Systemic vascular resistance averaged 1675 ± 157 in the congestive heart failure patients and 1338 ± 118 dyne s^{-1} cm^{-5} in the controls. Mean plasma renin activity of 4·9 ± 1·0 in the heart failure group was nearly twice that of 2·6 ± 0·4 ng/ml per hr in the control group.

RENIN AND HAEMODYNAMIC CORRELATES

Fig. 1 illustrates the relation between initial plasma renin activity and various haemodynamic indices for the 18 patients with congestive heart failure. The haemodynamic correlates examined were cardiac index, mean arterial and right atrial pressures, and mean pulmonary capillary wedge pressure.

Plasma renin activity and cardiac index did not correlate; the r value (excluding the controls) was 0·12. There was an inverse correlation ($P < 0{\cdot}05$) between renin and mean arterial pressure and renin and mean right atrial pressure; the r values were −0·48 and −0·52, respectively. The best correlation ($r = -0{\cdot}61$) for the patients with congestive heart failure was obtained between initial plasma renin activity and mean pulmonary capillary wedge pressure ($P < 0{\cdot}01$).

The values of the 5 control patients are also plotted on the figure but not included in the calculations. For cardiac index, mean arterial, and right atrial pressures they appear to be interspersed among the values of the patients with congestive heart failure. For the relation of renin to pulmonary capillary wedge pressure, however, the controls form a homogeneous group separate from the patients.

HAEMODYNAMIC RESPONSES TO SARALASIN

Fifteen patients with congestive heart failure received an infusion of saralasin. Nine (cases 6 to 14) responded with a decrease in mean arterial pressure, while in 6 (cases 15 to 20) it increased or did not change. Two types of pressure responses are illustrated in Fig. 2. In the patient shown in the left

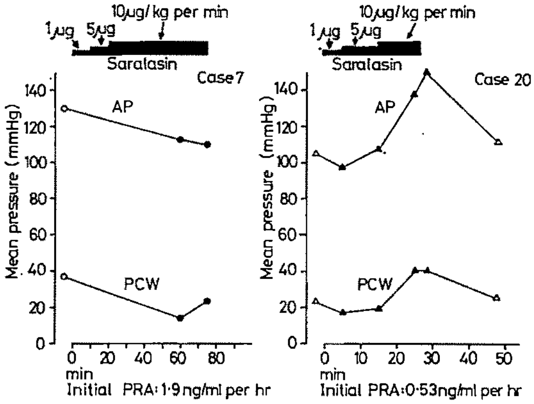

Fig. 2 *Responses of mean arterial and pulmonary capillary wedge pressure to saralasin infusion in 2 patients with congestive heart failure. Case 7 with 'normal' plasma renin levels had decreased pressures and case 20 with 'low' plasma renin activity had increased pressures.*

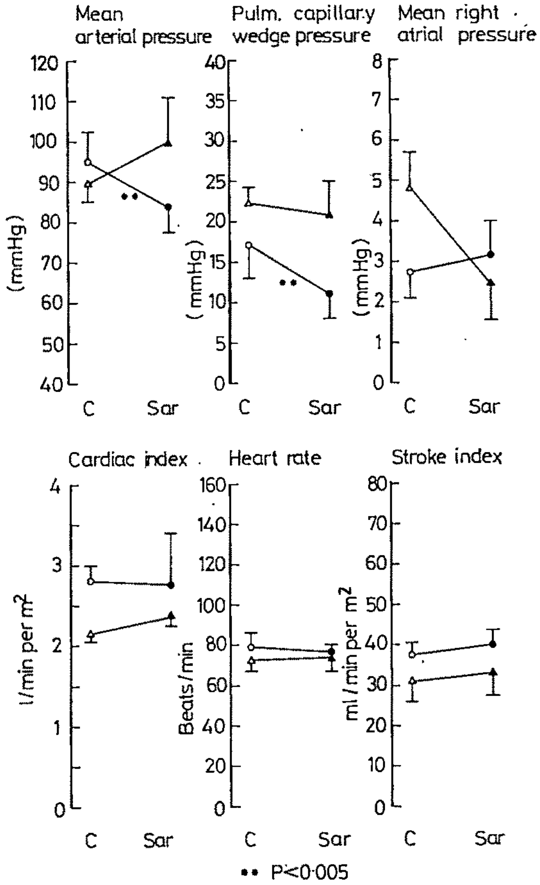

Fig. 3 *Haemodynamic correlates before (C, open symbols) and after (Sar, closed symbols) saralasin infusion. This shows patients who had decreases in blood pressure (circles) in response to saralasin and patients who experienced no change or an increase in their blood pressure (triangles). Pulmonary capillary wedge pressure decreased significantly (P < 0·005) in the patients whose mean arterial pressure decreased.*

panel (case 7) saralasin induced a decrease in mean arterial pressure of 20 mmHg. Simultaneously, mean pulmonary capillary wedge pressure fell by 13 mmHg. An opposite response is shown in the right panel of the same figure. In this patient (case 20) saralasin caused a progressive increase in mean arterial pressure of 50 mmHg, which returned to baseline within 30 minutes after stopping the infusion. Concurrent with mean arterial pressure, mean pulmonary capillary wedge pressure increased by 17 mmHg. In both patients heart rate hardly changed despite substantial changes in blood pressure (Table 2).

During saralasin infusion at a maximal rate of 10 µg/kg per min one patient (case 14) experienced profound hypotension which required immediate discontinuation of the procedure; subsequent recovery was uneventful. This patient is not included in the following analysis of the data. For the 8 others who experienced lower blood pressure in response to saralasin (Fig. 3), the mean decrease was 11·8 ± 2·8 mmHg (P < 0·005). The remaining 6 taken together had increases in their mean arterial pressure of 11·8 ± 8·0 mmHg. This overall increase was the result of a pressor response to saralasin in 3 (cases 18-20).

In the 8 patients in whom blood pressure fell, mean pulmonary capillary wedge pressure also decreased significantly from 17 ± 4·0 to 11 ± 3·1 mmHg (P < 0·005) during saralasin infusion (Fig. 3). In the same group right atrial pressure, cardiac index, heart rate, and stroke volume index hardly changed in response to saralasin. In the group of the 6 patients in whom blood pressure increased or did not change during saralasin, mean pulmonary capillary wedge pressure and heart rate remained unchanged. Right atrial pressure, cardiac index, and stroke volume index were not measured during saralasin infusion in case 20; in the remaining 5 patients these indices did not change significantly. Though not shown in Fig. 3, the haemodynamic indices of 4 controls did not change during saralasin infusion (Table 2).

Left ventricular function curves of all 13 patients in whom cardiac index was determined in response to saralasin are shown in Fig. 4. In a majority of the patients saralasin induced a distinct shift to the left, with either no change or even some increase in

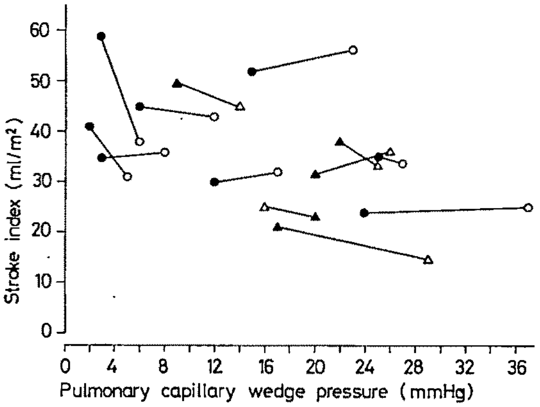

Fig. 4 *Left ventricular function curves of 13 patients who had an infusion of saralasin. Open symbols before and closed symbols after saralasin. (Circles and triangles: see Fig. 3). All but one patient who had increased arterial pressure experienced improvement in left ventricular function.*

stroke volume index, thus indicating improvement of their left ventricular function.

PLASMA RENIN ACTIVITY IN SUBGROUPS DEFINED BY SARALASIN RESPONSE

Fig. 5 shows initial plasma renin levels of all patients replotted according to their arterial pressure response to saralasin. The 6 who did not decrease their arterial pressure showed a mean plasma renin of 2·0 ± 0·58 ng/ml per hr. In contrast, the 8 patients who responded to saralasin by a fall in arterial pressure had a significantly higher initial mean plasma renin activity of 8·1 ± 1·6 ng/ml per hr (P < 0·01). Mean renin level for the 5 controls was 2·6 ± 0·43 ng/ml per hr.

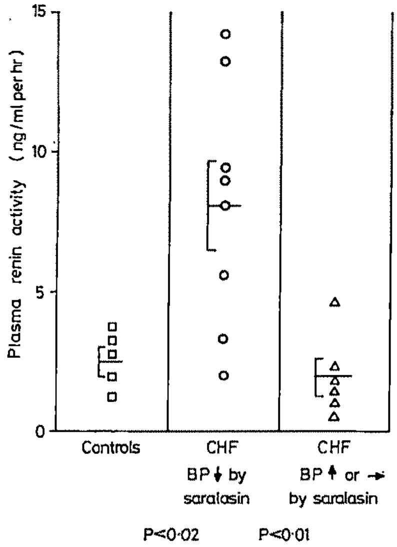

Fig. 5 *Initial plasma renin activity of controls (□), and patients with congestive heart failure who had a decrease (○) or no change or an increase (△) in arterial pressure in response to saralasin infusion. The patients who had a decrease in blood pressure had significantly higher renin levels (P < 0·01).*

Not shown in Fig. 5 is the renin response to saralasin infusion. The 6 patients hardly increased plasma renin activity to 3·4 ± 1·8 ng/ml per hr whereas the 8 patients who had decreased arterial pressure showed a substantial increase to 24 ± 6·1 ng/ml per hr (P < 0·02). No significant change was observed in the controls.

Discussion

The purpose of this study was to assess the role of the renin-angiotensin system in patients with congestive heart failure by measuring renin levels and by determining the effect of specific angiotensin II blockade on various haemodynamic indices. No relation between initial plasma renin activity and cardiac index was found but some inverse correlations were observed between plasma renin and either mean arterial pressure or right atrial pressure. The strongest inverse correlation existed between initial plasma renin activity and mean pulmonary capillary wedge pressure. When saralasin was infused into 15 of the patients, 9 responded with a decrease in arterial pressure, 1 of whom developed acute hypotension which was quickly reversed by administration of saline. Three had no change in their arterial pressure and 3 had increases, thus exhibiting an agonistic response to saralasin. Heart rate was not predictably influenced by the change in arterial pressure. Mean plasma renin activity of the patients who lowered blood pressure in response to saralasin was significantly higher than that of the patients who either did not change or increased it. Plasma renin activity in the latter group was not different from that of the 5 controls. The 2 patients who experienced the most striking agonistic response to saralasin had the lowest renin values of all. In all but these 2 patients, saralasin decreased mean pulmonary capillary wedge pressure without reducing stroke volume in most. In some, left ventricular function was substantially improved by a simultaneous increase in stroke volume and reduction of mean pulmonary capillary wedge pressure.

Renin via angiotensin II plays a direct role in sustaining blood pressure in some patients with congestive heart failure. This is illustrated by those 9 patients with higher renin levels who responded to saralasin with a blood pressure reduction. At the same time, the inverse correlation between plasma renin activity and arterial pressure suggests that the renin-angiotensin system in such patients may, at least in part, be stimulated by a relative decrease in arterial pressure. The majority of our patients had been treated with diuretics as shown in Table 1. Studies in animals (Gavras *et al.*, 1973), normal volunteers (Sancho *et al.*, 1976; Posternak *et al.*, 1977), and hypertensive patients (Brunner *et al.*, 1974b; Gavras *et al.*, 1976) have shown that blood pressure becomes more renin dependent during sodium depletion. However, it appears from Table 1 that previous administration of diuretics did not predict blood pressure responsiveness to saralasin. The effectiveness of diuretics varies among patients with congestive heart failure and therefore those 9 patients who responded to saralasin with a blood pressure drop could have developed more diuretic-induced hypovolaemia. This latter possibility is in part supported by the slightly lower mean right atrial pressure of these patients. Thus, blood pressure responsiveness to saralasin may have been accentuated by diuretic therapy and its influence on intravascular volume and renin secretion. However, 2 of the patients (cases 9 and 11) who had not received any diuretics also lowered their blood pressure, thus suggesting that renin dependency was not only the result of diuretic therapy. This is supported by findings in animals with experimental heart failure, which received no diuretics. In them blood pressure also was renin dependent unless excessive sodium and water were retained (Watkins *et al.*, 1976; Morris *et al.*, 1977).

Recently Nicholls and coworkers reported that diuretics other than spironolactone hardly increase renin levels when administered long term to patients with congestive heart failure (Nicholls *et al.*, 1976). Our data are in total agreement since renin levels did not differ when comparing patients treated with (4·3 ± 1·8) or without such diuretics (4·1 ± 1·7). Furthermore, the 5 patients on spironolactone had slightly higher renin levels (6·8 ± 1·4) though the difference was not statistically significant. If the observed correlation between plasma renin activity and pulmonary capillary wedge pressure is analysed similarly, it appears that the strongest correlation ($r = 0{\cdot}75$) was seen in the patients receiving no diuretics and the weakest ($r = 0{\cdot}60$) in the 5 patients on spironolactone. Thus, taken together, there is strong evidence suggesting that the observed relation between renin and cardiac function is physiologically meaningful.

Mean pulmonary capillary wedge pressure reflects left ventricular function and venous return. Venous return is determined by total blood volume and its fractional distribution between the arterial and venous sides of the circulation. In our study, the strongest inverse correlation was observed between plasma renin activity and pulmonary wedge pressure; renin was high unless pulmonary capillary wedge pressure was much increased. Thus, it seems that renin levels of patients with congestive heart failure are inappropriately high but may be returned toward normal by the compensatory mechanism of increasing preload. This is supported by recent findings in experimental heart failure (Watkins *et al.*, 1976; Morris *et al.*, 1977). In stable, chronic congestive heart failure it would then be understandable that renin levels do not correlate with cardiac index when compensating mechanisms are in full play. This is because cardiac output at rest is often kept at normal levels by a compensatory rise in preload which in turn modulates renin secretion, possibly via cardiopulmonary receptors (Zehr *et al.*, 1976).

The decrease in mean pulmonary capillary wedge pressure in response to saralasin seen in 12 of 14 patients may be attributed in 8 to the concomitant reduction of arterial pressure which is the principal determinant of afterload. In 4 others however, pulmonary capillary wedge pressure decreased in spite of no change or even a slight increase in arterial pressure. Enhanced left ventricular contractility could explain this decrease, but experimental evidence available to date suggests that angiotensin II, if it has any effect on myocardial contractility *in vivo*, would tend to increase it (Downing and Sonnenblick, 1963; Koch-Weser, 1965). Hence, saralasin should reduce inotropy unless it exerts an agonistic effect on the myocardium. To our knowledge no data are available demonstrating a direct effect of saralasin on myocardial contractility. Another possible explanation of the decrease in mean pulmonary capillary wedge pressure could be an increase in left ventricular compliance. The respective roles of changes in compliance and in left ventricular end-diastolic volume cannot be differentiated by the method used in the present study (Braunwald and Ross, 1963).

The most tempting interpretation of the results would be that saralasin blocks a direct vasoconstrictor effect of renin via angiotensin II on the venous capacitance vessels. Reduced venous tone would explain the simultaneous decrease in cardiac index and mean arterial pressure in the face of an increase in systemic vascular resistance observed in some patients, for example cases 8 and 12. A direct vasoconstrictor effect of angiotensin II on the veins was described by some workers (Emerson *et al.*, 1965; Dollery *et al.*, 1963), but others were unable to confirm these observations (Borucki *et al.*, 1976).

Our results nevertheless suggest that this mechanism may be operative in patients with congestive heart failure.

Improvement in cardiac function during saralasin infusion observed in many of our patients raises the question whether angiotensin antagonists have therapeutic potential in congestive heart failure. In recent years, several studies have shown the benefit of afterload reduction by drugs such as glyceryl trinitrate, nitroprusside, and phentolamine (Chatterjee and Parmley, 1977). It is now known that these agents also affect preload to a variable degree, thus accounting for disparate modification of left ventricular function (Miller *et al.*, 1976). Depending on the initial haemodynamic status, changes may result predominantly from a decrease in preload or in impedance, or both. It should be noted that most of these studies (Franciosa *et al.*, 1972; Gold *et al.*, 1972; Chatterjee *et al.*, 1973; Gould *et al.*, 1974; Perret *et al.*, 1975) were done in patients with acute heart failure after myocardial infarction. Such patients, who often have reduced cardiac output, differ from those included in our study who had stable chronic congestive heart failure.

Recent work has shown a therapeutic benefit of vasodilators even in chronic congestive heart failure (Cohn *et al.*, 1974; Kovick *et al.*, 1976). Angiotensin inhibition by its inherent specificity may have the advantage of fewer side effects. The one severe problem encountered, that is a blood pressure increase of 50 mmHg in case 20, would probably have been avoidable by using smaller doses of saralasin, for example 1 to 2 μg/kg per min.

Even more promising could be the use of specific antagonists of angiotensin converting enzyme rather than saralasin (Ondetti *et al.*, 1971). They lack agonistic properties which would avoid a major adverse effect that we encountered with saralasin, that is, blood pressure increase. Furthermore, converting enzyme inhibition has been shown in hypertensive patients to be more effective in lowering blood pressure (Gavras *et al.*, 1974; Case *et al.*, 1976; Gavras *et al.*, 1977). Accordingly, even more load reduction might be expected with these compounds in patients with congestive heart failure. A new specific antagonist of angiotensin converting enzyme has recently been tested which has the additional advantage of being orally active (Ferguson *et al.*, 1977; Ondetti *et al.*, 1977). Thus, this agent will allow prolonged specific angiotensin inhibition. Prolonged rather than acute blockade of the renin-angiotensin system could provide the further advantage of reducing angiotensin-dependent aldosterone secretion. Angiotensin inhibition may then combine a direct effect on vasomotor tone with simultaneous decrease in blood volume.

Taken together, patients with chronic congestive heart failure appear to have inappropriately high plasma renin activity which tends to return toward normal depending on the compensatory rise in preload. This points to an interaction between cardiac function and venous return modulating renin secretion, possibly via cardiopulmonary receptors. Inhibition of the renin-angiotensin system may decrease preload and impedance and thereby improve cardiac function. Specific angiotensin inhibitors deserve further trials to evaluate their usefulness for the treatment of congestive heart failure.

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Effect of prolonged intensive training on cardiorespiratory response in patients with angina pectoris

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SUMMARY The cardiorespiratory response to prolonged work was investigated in 15 patients (age 51 ± 5·6) after transmural myocardial infarction; the patients had angina pectoris. Based on an individually determined pain threshold heart rate the following two relative work loads were obtained; 55 per cent and 90 per cent of threshold heart rate. Training was monitored using the 10-channel Siemens radio-telemetry system, and consisted of 30 minutes continuous pedalling, twice per week. Pretraining results showed a substantial increase in heart rate (HR 12 ± 8·2) and systolic blood pressure (SBP 15 mmHg) between the 5th and the 10th minute of work and decrease in O_2 consumption (Vo_2 l/min) and O_2 pulse between the 15th and 30th minute of exercise.

Training resulted in the following changes: Decreased heart rate at rest and during work ($P \leqslant 0·01$). Systolic blood pressure did not rise up to the 15th minute of work. Oxygen consumption increased gradually, reaching a steady state after 15 minutes of work. O_2 pulse increased gradually and remained constant during the last 15 minutes of work. SBP × HR product decreased significantly ($P \leqslant 0·05$-$0·01$) at rest and during work. Favourable changes in minute ventilation and ventilation equivalent indicate improved respiratory adjustment. Clinically there was a pronounced decrease in severity and frequency of angina pectoris along with increased work time before onset of pain. The data show that intensive prolonged training may result in improvement of the physiological adaptive mechanism of patients with angina pectoris to continuous physical stress.

In most of the studies of exercise capacity of patients with angina pectoris, work periods have been short lasting several minutes only (Eckstein, 1957; Jones and Reeves, 1968; Redwood *et al.*, 1972; Kennedy *et al.*, 1976). For many years we have been interested in the physiological effect of prolonged intensive training on the adaptive mechanism to exertion in angina pectoris patients. The aim of the present investigation was to study the cardiorespiratory adjustment to prolonged work periods in angina patients, and to evaluate the effect of the improved physical work capacity on the related measurements.

Subjects and methods

Fifteen men with angina pectoris (aged 51 ± 5·6 yr), 14 after transmural myocardial infarction and one without previous infarction, were under observation for a 4-month period. All patients had typical ischaemic electrocardiographic changes, with 1 mm horizontal ST segment depression during or shortly after physical exertion. These patients had previously participated in a calisthenic-type exercise programme lasting for approximately a year. At the conclusion of this programme, none of the patients showed significant improvement in any of the measured variables related to the cardiorespiratory system. Additional testing was conducted before (T1) and after 4 months (T2) of intensive ergometric training. Since true maximal heart rate and oxygen consumption could not be attained by these patients, a pain threshold heart rate was determined for each patient at the onset of anginal pain (Kellermann, 1975). Two exercise loads were then determined for each patient, the first 55 per cent of each threshold and the second 90 per cent of pain threshold heart

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rate. The following observations were made during exercise testing[1]: heart rate, brachial arterial blood pressure, expired gas collection (Kofranyi respirometer) and electrocardiogram at rest, after 5 minutes of pedalling at 55 per cent of the patient's pain threshold heart rate, after 10 minutes at 90 per cent of the patient's pain threshold heart rate, and after 25 minutes at this latter load. Recovery heart rate and blood pressure were measured 3 and 5 minutes after cessation of exercise. Measurements of O_2 consumption were made at least twice and the results averaged, in order to reduce possible methodological errors.

The following values were calculated:

$$O_2 \text{ pulse} = \frac{O_2 \text{ consumption (ml/min)}}{\text{HR}}$$

Ventilation equivalent =

$$\frac{\text{Minute ventilation}}{O_2 \text{ consumption (ml/min)}} \times 100$$

Double product = Systolic BP × HR (Sarnoff *et al.*, 1958)

$$\text{Respiratory quotient} = \frac{CO_2 \text{ produced}}{O_2 \text{ consumption}}$$

Room temperature was maintained at 22 ± 1°C.

The test was discontinued in the event of increasing chest pain, other subjective complaints (dizziness, dyspnoea), additional pathological electrocardiographic adnormalities (ST depression exceeding 3 mm, arrhythmias, multifocal increasing frequency of early cycle ventricular premature contractions), or consistent decrease in systolic blood pressure, or after completion of 30 minutes continuous pedalling.

TRAINING

The *calisthenic programme* included breathing exercises, muscular relaxation, non-competitive ball games, gymnastics, and running twice weekly with an energy expenditure of 2 to 9 cal/min. The annual programme consisted of the following phases:

(1) 1st to 10th week, slow rate low intensity exercises in supine position emphasising continuous breathing and long recovery periods between exercises. Walking at individually convenient rate for 5 to 10 minutes.

(2) 11th to 20th week, introducing some muscle strength exercises, increasing variety of exercises, and increasing speed and duration of walking.

(3) 21st to 30th week, increasing rate and intensity of exercise performed, decreasing recovery time between exercises, short jogging periods (10 to 30 s), and non-competitive games.

(4) 31st to 50th week, increasing time of jogging (1 min) and intensity of floor exercises, exercises in erect position.

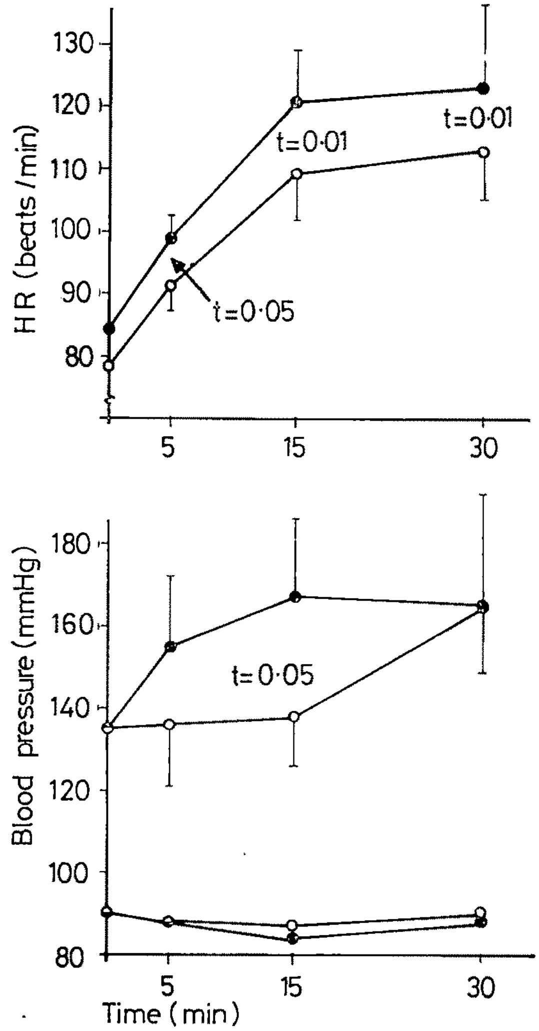

Fig. 1 *Heart rate and blood pressure during prolonged work before* (●——●) *and after* (○——○) *4 months of intensive training.*

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[1] *Multistage, near maximal ergometric test.* After detailed physical examination and resting electrocardiogram, the test normally started with a 25-Watt load with subsequent 25-Watt increments. Each phase of work was of 5 minutes duration, followed by a 5-minute rest period. The following age-related target heart rates were used: 20 to 39 years, 170/min; 40 to 59 years, 150/min; 60 years and over, 130/min.

Table 1 *Circulatory measurements in patients with angina pectoris before and after a 4-month intensive ergometric training programme*

Load and time	*HR (beats/min)*		*P*	*Blood pressure (mmHg)*		*P*	*SBP × HR*		*P*
	Before	*After*		*Before*	*After*		*Before*	*After*	
Rest	83 ± 11·3	78 ± 8·08	NS	135/90 ± 17·5/9·9	135/90 ± 15·7/8·7	NS	12 057 ± 2 655	10 549 ± 1 296	NS
5 min at 55 per cent of pain threshold heart rate	109 ± 4·0	92 ± 4·0	< 0·01	155/88 ± 17·8/8·0	136/87 ± 15·0/10·0	NS	14 134 ± 1 647	12 191 ± 1 796	< 0·05
10 min at 90 per cent of pain threshold heart rate	121 ± 8·2	109 ± 8·8	< 0·01	167/84 ± 19·4/8·7	138/87 ± 13·7/8·3	< 0·05	20 364 ± 3 018	17 501 ± 2 100	< 0·01
25 min at 90 per cent of pain threshold heart rate	123 ± 14·5	113 ± 8·1	< 0·05	164/87 ± 18·3/8·8	164/89 ± 17·3/8·6	NS	20 916 ± 3 610	18 419 ± 2 333	< 0·01

NS, not significant.

Table 2 *Oxygen consumption (Vo_2) and O_2 pulse in patients with angina pectoris before and after 4-month intensive ergometric training programme*

Load and Time	*O_2 pulse (ml O_2/beat)*		*P*	*Vo_2 l/min*		*P*
	Before	*After*		*Before*	*After*	
Rest	4·2 ± 1·4	4·4 ± 1·04	NS	0·343 ± 0·020	0·342 ± 0·025	NS
5 min at 55 per cent of pain threshold heart rate	7·7 ± 1·8	8·7 ± 1·5	< 0·05	0·764 ± 0·058	0·764 ± 0·065	NS
10 min at 90 per cent of pain threshold heart rate	9·8 ± 1·5	9·9 ± 1·8	NS	1·230 ± 0·101	1·038 ± 0·095	< 0·05
25 min at 90 per cent of pain threshold heart rate	8·9 ± 1·7	9·8 ± 2·0	< 0·05	1·119 ± 0·100	1·100 ± 0·090	NS

NS, not significant.

Ergometric training lasted 4 months and took place twice weekly, always during the morning. Using the Monark bicycle ergometer, the first 5 minutes of pedalling (to 55% of pain threshold heart rate) were considered as 'warm up'. This was followed without a pause by the next load (to 90% of pain threshold heart rate) for 25 minutes. A constant rate of pedal revolutions was not required, but was generally seen to be 50 ± 10 revolutions/min. The patient's electrocardiogram was monitored using the 10-channel radiotelemetry system of Siemens Telecust.

STATISTICAL METHOD

Standard deviation was calculated by methods using the ungrouped data procedure, while the differences between the means and levels of significance were obtained using Student's t test for small samples (Guilford, 1965).

Results

The results are presented in Tables 1 and 2 and Figs 1 and 2.

HEART RATE

The prescribed ergometric training resulted in a significantly ($P < 0{\cdot}01$) lower heart rate during exercise at similar work loads.

BLOOD PRESSURE

Comparison between T1 and T2 showed that ergometric training did not change systolic blood pressure at rest or at the end of exercise. During exercise in T1, systolic blood pressure rose substantially (20 mmHg) after 5 minutes of work at the warm-up level (55% pain threshold heart rate). Further rises were recorded when the load was increased to 90 per cent and throughout the next 10 minutes. During T2, systolic blood pressure remained essentially constant until the 15th minute of work, after which a significant increase of 25 mmHg was observed (Fig. 1). No changes in diastolic blood pressure were observed during any phase of exercise in either T1 or T2 (Table 1).

O_2 PULSE

Training did not significantly affect oxygen consumption at the individually limited levels (Table 2,

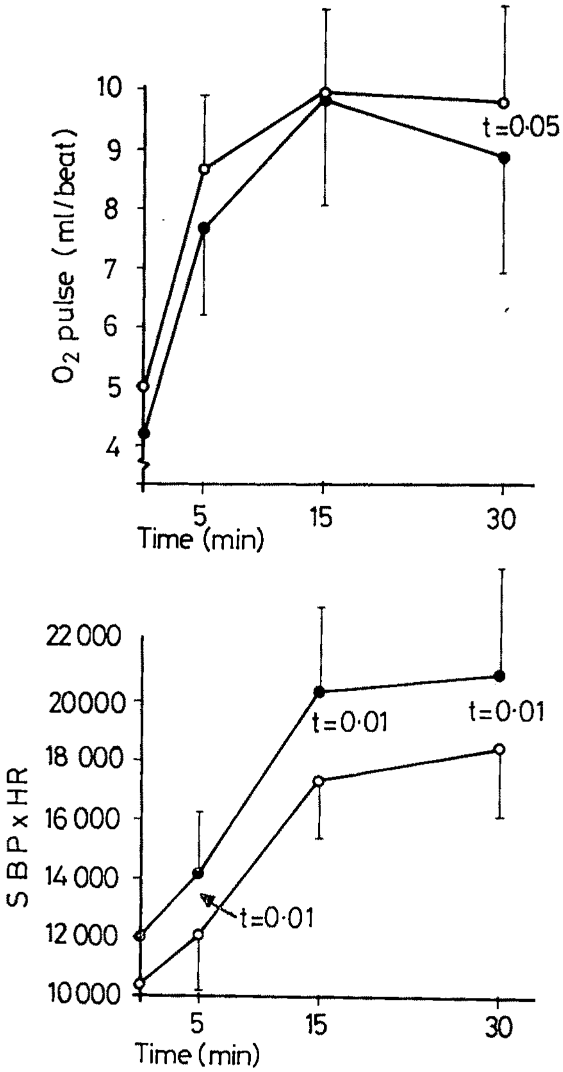

Fig. 2 *Oxygen pulse and double product during prolonged work before* (●———●) *and after* (○———○) *4 months of intensive training.*

Fig. 2). A reduction of 111 ml/min was observed between the 10th and 25th minute of exercise, but only in T1. During T2, oxygen consumption increased gradually, reaching a 'steady state' level after about 20 minutes. Relating oxygen consumption to heart rate, O_2 pulse increased similarly before and after training up to the 15th minute of work (Table 2, Fig. 2). From this point up to the end of exercise, there was a decrease of 0·9 ml in O_2 pulse in T1, while in T2 O_2 pulse remained constant. Systolic blood pressure × heart rate (double product), which is generally accepted as an indirect estimation of the myocardial oxygen consumption (MVo_2) (Sarnoff *et al.*, 1958), was significantly ($P < 0{\cdot}01$) lower after training (Table 2, Fig. 2). A reduction of about 2000 arbitrary units from T1 to T2, both at rest and during each phase of exercise, reflects a decrease in myocardial work.

VENTILATORY MEASUREMENTS

The ergometric training resulted in slight improvement in ventilation, ventilation equivalent, respiratory quotient, and energy expenditure during the various phases of training, but these changes were not statistically significant.

Discussion

The ability to perform continuous exercise depends basically on adequate supply of oxygenated blood and fuel for combustion for the working muscles. It is well established that cardiac output increases in proportion to work demands and then remains constant, both in healthy sedentary males and in coronary patients (Wade and Bishop, 1962; Ekelund and Holmgren, 1964; Ekelund *et al.*, 1967; Hartley *et al.*, 1969). However, the time course of cardiac output adaptation was found to be faster in healthy subjects (Jones and Reeves, 1968). Though cardiac output values during continuous submaximal work are similar in healthy men and in coronary patients, the total output of oxygenated blood during an exercise period is greater in normal men.

Ekelund *et al.* (1967) reported an increase of 30 beats per minute (bpm) between the 10th and the 60th minute of work. Grimby *et al.* (1966) found an increase of 10 to 12 bpm and Ekblom (1970) 20 bpm during an hour of pedalling. In this study, heart rate increased by 10 to 12 bpm only up to the 15th minute of work. This difference is not significant and can in part be attributed to differences in age, fitness level, and relative work load. As heart rate increases, stroke volume decreases at moderate and even low work loads (Levy *et al.*, 1961; Cobb and Johnson, 1963; Saltin and Stenberg, 1964; Ekelund, 1967; Sowton and Burkart, 1969; Redwood *et al.*, 1972). These circulatory changes, resulting from decreased cardiac filling, which is a consequence of the lower tone of the capacitance vessels (Ekelund and Holmgren, 1964), are basically similar in healthy subjects and in coronary patients.

Data on the favourable effect of training on myocardial function have not been consistent. Several investigators, most of whom have used moderate exercise routines, reported unimproved left ventricular function (Redwood *et al.*, 1972; Kennedy *et al.*, 1976). On the other hand it seems that prolonged intensive or hypoxic training conditions result in improved myocardial performance (dP/dt max) and triple product (Monroe, 1964; Scheur and Stezoski, 1972; Scheur *et al.*, 1974; Alexander and Liu, 1976; Carey *et al.*, 1976; Sturzenhoffcker *et al.*, 1976). In our study, patients were rarely stopped during exercise. Usually they were told to continue pedalling and were asked to stop only if there were increasing chest pain and/or ST depression exceeding 3 mm. Blood pressure during continuous submaximal exercise has been described in healthy men (Holmgren, 1956; Hartley *et al.*, 1969; Granath *et al.*, 1970). In contrast to healthy subjects, coronary patients in our study showed a steady increase in systolic blood pressure during T1. Training resulted in significantly lower systolic blood pressure from the start up to the 15th minute of exercise, suggesting a reduction in total vascular resistance and contractile work of the left ventricle during this time. It is interesting to note that changes in blood pressure and heart rate were not as pronounced in patients with angina pectoris who were participating in a calisthenics and game-type programme (Kennedy *et al.*, 1976) or other coronary rehabilitation programme reviewed by Detry (1973). True maximal oxygen consumption was not attained by these patients; symptom-limited oxygen consumption increased by 8 to 10 per cent, as in several other studies involving coronary patients (Detry, 1973). The decrease in oxygen consumption during the last 15 minutes in T1 resulted in decreased O_2 pulse. This suggests a decreased blood flow to the myocardium which was not evident after training.

Ventilatory measurements showed slight but not significant changes similar to those obtained after training in healthy men. In addition, it may be assumed that local peripheral changes, increasing the arteriovenous oxygen difference, occurred in our patients also.

Clinically, there was a decrease in the severity and frequency of angina pectoris in almost every patient who underwent ergometric training. The patients described less severe pain with slower progression; they could often continue to work and walk without taking glyceryl trinitrate and could do more work before the onset of anginal pain.

In conclusion, we found that intensive training improved cardiorespiratory function and enabled coronary patients to do prolonged work more efficiently. The improved central and peripheral circulatory adaptation is responsible for the decrease in the physiological response to exercise and consequent relief of anxiety and lack of confidence of untrained angina patients during prolonged exercise. The fact that none of the patients dropped out of the training is attributed to the good physiological response, high motivation, group co-operation, and the excellent relation between the group and the medical team.

The authors thank Mrs P. Nachum, R.N., for her work in supervising the training programme.

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Use of amiodarone in bradycardia-tachycardia syndrome

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SUMMARY Five patients with the bradycardia-tachycardia syndrome have been treated successfully with the antiarrhythmic agent amiodarone. Three patients were treated for over nine months and one of these patients had corneal micro deposits. One patient had to be taken off the drug because of side effects. Amiodarone should be tried in patients suffering from the bradycardia-tachycardia syndrome before resorting to cardiac pacing.

Bradycardia-tachycardia syndrome usually reflects the presence of sinoatrial disease, in which episodes of supraventricular tachycardia complicate sinus bradycardia with or without periods of sinus arrest or sinoatrial block.

Dizziness, syncope, or convulsions may result from cerebral ischaemia secondary to bradycardia, and tachycardia may cause palpitation, ischaemic cardiac pain, dyspnoea, and, more rarely, hypotension and cardiac failure. Systemic emboli may occur particularly in patients over 50 years (Rubenstein *et al.*, 1972; Ferrer, 1973).

The aetiology of the sick sinus syndrome and the bradycardia-tachycardia syndrome is often unknown, but associations with coronary artery disease, thyrotoxicosis, cardiomyopathy, amyloidosis, diabetes, and cardiac surgery have been reported, and there is a rare familial form (*British Medical Journal*, 1977).

Correlation of electrocardiographic rhythm changes with symptoms over 24-hour periods using ambulatory monitoring equipment facilitates diagnosis of the syndrome, and the combination of implanted pacemakers and appropriate antiarrhythmic agents has been successful in controlling the clinical features. Drug treatment alone is difficult since agents which control the tachycardia may aggravate the bradycardia and vice versa. The ideal drug would be effective in controlling bradycardia and tachycardia without the need for cardiac pacing, and in this communication we report the results of treating 5 patients with the antiarrhythmic agent amiodarone.

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Case reports

CASE 1

A 54-year-old man was admitted in September 1974 with an acute anterior myocardial infarction complicated by ventricular fibrillation and atrial fibrillation. He had received methyldopa for 6 years previously for essential hypertension. In June 1976, he was readmitted with bouts of ischaemic cardiac pain associated with periods of rapid atrial fibrillation followed by sinus bradycardia at 30 beats a minute. Treatment with digoxin, verapamil, and propranolol in turn caused sinus bradycardia associated with faintness and dizziness, and failed to prevent periods of atrial fibrillation.

Amiodarone 200 mg twice daily was started in July 1976, and was subsequently reduced to 100 mg twice daily because of nausea. He has had no further bouts of chest pain, dizziness, faintness, or palpitation and has now taken the drug for 13 months. Corneal micro deposits were noted 5 months after starting amiodarone, but have not increased since, and have not interfered with vision. The condition was explained to the patient who expressed a desire to continue with the drug. A 24-hour electrocardiographic recording using the Oxford Medilog equipment showed no arrhythmia one year after the start of treatment.

CASE 2

A 73-year-old man was admitted to hospital in July 1976 with a 3-month history of retrosternal pain variably related to exertion. For 2 days before admission he had suffered from repeated episodes of dizziness and inability to concentrate, and on one occasion had lost consciousness resulting in a fall and a scalp laceration. He had been treated with guanethidine and a thiazide diuretic for two years previously.

On admission his blood pressure was 180/100 mmHg, with a basal midsystolic murmur and the electrocardiogram showed left ventricular hypertrophy and prolonged bouts of atrial tachycardia at 150 beats a minute, and sinus bradycardia at 40 beats a minute. The slow rhythm was associated with dizziness and feelings of syncope.

Digoxin caused persistent sinus bradycardia and verapamil was subsequently tried without altering the frequency of the tachycardia and bradycardia. Amiodarone 200 mg twice daily successfully controlled the symptoms, and routine, regular 12 lead electrocardiograms have shown sinus rhythm. A 24-hour electrocardiogram in June 1976 shows sinus rhythm with a rate which drops to 46 a minute on occasions with no symptoms.

CASE 3

A 48-year-old woman was investigated in September 1976 for a pyrexial illness. Chest *x*-ray film showed diffuse pulmonary infiltration, and the ESR was 50 mm/hour (Westergren). A diagnosis of allergic alveolitis was made, and she was treated with prednisolone. In December 1976 she was admitted because of transient loss of consciousness, and a routine electrocardiogram showed the features of the bradycardia-tachycardia syndrome with sinus bradycardia at 30 beats a minute coinciding with transient loss of consciousness. A trial of propranolol caused extreme bradycardia and because of previous success in this condition, amiodarone 200 mg twice daily was started and sinus rhythm was restored, with no further loss of consciousness.

Six weeks later the amiodarone was withdrawn without return of symptoms and she has remained well subsequently.

CASE 4

A man aged 87 years was admitted in October 1976 with a 6-week history of transient disturbance of consciousness and short periods of lower sternal tight feelings. A 24-hour electrocardiogram using the Oxford Medilog system showed periods of supraventricular tachycardia at 140 per minute associated with retrosternal discomfort, and periods of sinus bradycardia at 40 a minute coinciding with disturbance of conscious level (see Fig.). Treatment with phenytoin made no difference to the clinical features and amiodarone 200 mg twice daily was started 3 weeks later with complete abolition of symptoms during subsequent 9 months on the drug.

CASE 5

A woman aged 47 years was first seen in 1970 with paroxysmal supraventricular tachycardia occurring particularly at night. The patient reported pulse rates at under 40 a minute on other occasions. She was treated unsuccessfully with courses of propranolol, phenytoin, and procainamide, and periods of sinus bradycardia were seen to be associated with exhaustion and feelings of faintness. In January 1977, her blood pressure was 125/80 and a 24-hour electrocardiogram showed periods of sinus tachycardia at 130 a minute alternating with sinus bradycardia at 32 a minute and sinus arrest. She was started on amiodarone 200 mg twice daily, with no improvement, but on 200 mg three times per day she had no cardiac symptoms, and a repeat 24-hour electrocardiogram showed sinus rhythm varying between 60 and 84 beats a minute. She complained of feeling unwell without specific features, and blood pressure rose to 190/125 mmHg. Amiodarone was stopped after 10 weeks but the blood pressure remained high, and she has been on hypotensive agents since. The palpitation and exhaustion associated with bradycardia have persisted, and she is awaiting permanent cardiac pacemaking.

Discussion

Amiodarone is a benzofuran derivative which was originally introduced as an antianginal agent, but has subsequently been shown to be valuable in the management of atrial and ventricular arrhythmias and in the Wolff-Parkinson-White syndrome (Rosenbaum *et al.*, 1976). There have been no previous reports of the use of amiodarone in the bradycardia-tachycardia syndrome.

The principal actions of amiodarone are to cause relaxation of vascular smooth muscle resulting in a slight fall in systemic vascular resistance with slight reduction in systemic blood pressure, and a fall in coronary arterial resistance and improved coronary blood flow. The drug also causes an atropine-resistant bradycardia, and reduces the effects of catecholamines and sympathetic stimulation without acting as a competitive α and β receptor blocking agent. Singh and Vaughan Williams (1970) report that amiodarone causes prolongation of the duration of the action potential in atrial and ventricular muscle with no change in the resting potential, and amiodarone has been grouped with bretylium as a class 3 antiarrhythmic agent (Olsson *et al.*, 1973; Singh and Hauswirth, 1974). The net haemodynamic effects of the drug are an increase in coronary arterial blood flow, and reduction in left ventricular work and in myocardial oxygen consumption owing to the slowing of the heart and to

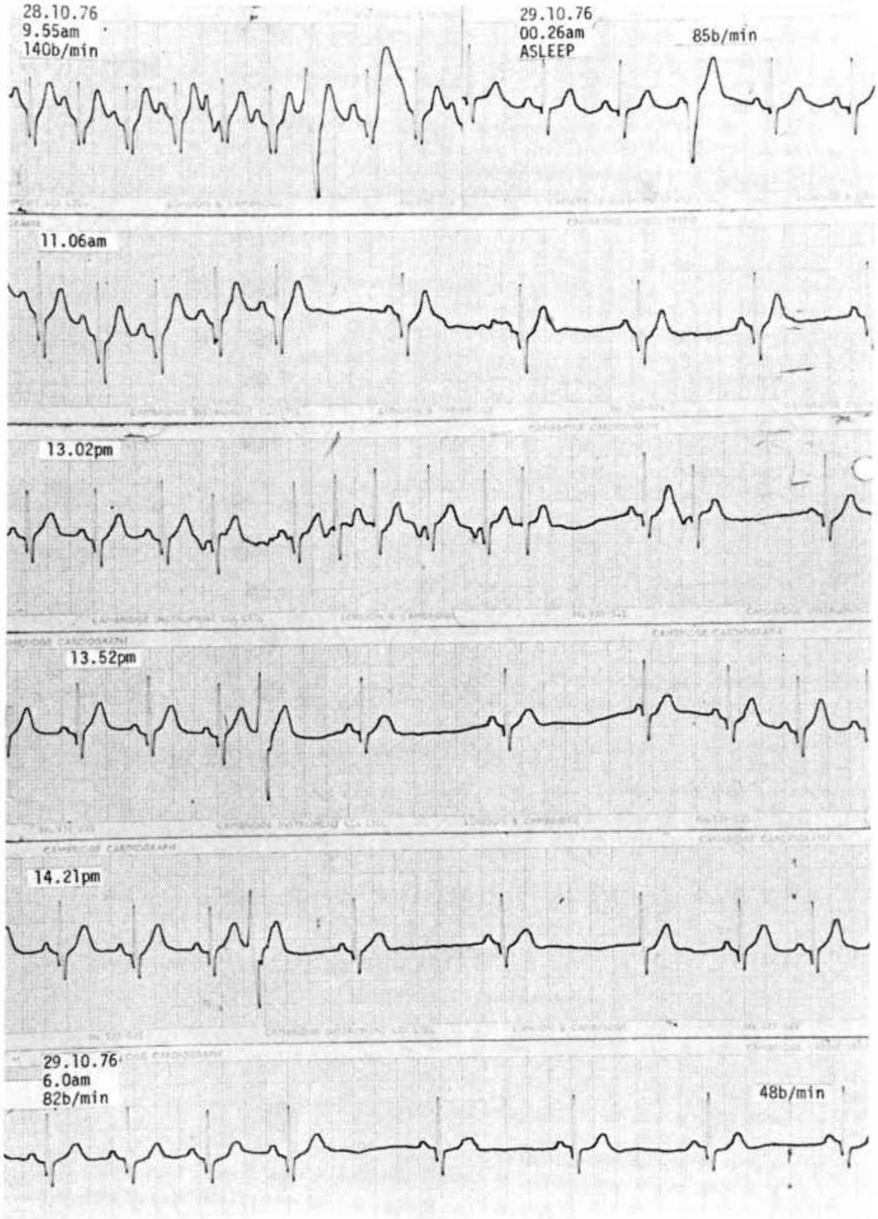

Fig. *Twenty-four hour electrocardiogram from case 4 showing supraventricular tachycardia and sinus bradycardia.*

the reduction in systemic vascular resistance (Charlier *et al.*, 1972).

There is ample evidence of the efficacy of amiodarone in the management of arrhythmias, particularly of supraventricular origin (Van Schepdael and Solvay, 1975; Rosenbaum *et al.*, 1976), but its use has been limited because of concern over side effects. Bradycardia, thyroid disorders, skin lesions, photosensitivity, and one case of sensory ataxic paraesthesiae and tremor have been described (Lustman and Monsea, 1974), but most concern has centred on the frequency of corneal micro deposits. The deposits, however, are usually found below the pupil, do not interfere with vision, are reversible, and may be prevented by methylcellulose eye drops (Francois, 1969; Soussi and Colonna, 1974).

One patient, case 1, has developed corneal micro deposits without interference with vision, and 2 patients have stopped amiodarone. Case 3 has remained well after 6 weeks on the drug and 1 patient, case 5, felt generally unwell on amiodarone and her blood pressure rose significantly, so the drug was withdrawn after 10 weeks. In view of the usual hypotensive effect of amiodarone, the rise in blood pressure in this patient is surprising and unexplained, but may be a coincidental finding and not a true complication of therapy.

The most important finding in these 5 patients is that none of them developed symptomatic bradycardia despite taking adequate amiodarone to prevent supraventricular tachycardia. Failure of the drug to produce excessive slowing of the heart may reflect improved coronary arterial blood supply because of amiodarone-induced relaxation of smooth muscle in the coronary arteries. The sinus node is supplied by a single vessel arising from either the right coronary artery or the left circumflex artery, and improved blood flow through the sinus node artery as a result of amiodarone administration may improve perfusion of the sinus node, and the atrial myocardium and interatrial septum which receive blood supply via the same vessel. In 3 of the 5 patients in this series, ischaemic heart disease is the probable cause of the bradycardia-tachycardia syndrome and improved coronary arterial blood flow by amiodarone could aid atrial bradycardia in these patients.

We suggest that amiodarone deserves a trial in patients suffering from the bradycardia-tachycardia syndrome before they are committed to permanent cardiac pacemaking.

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Disappearing His deflection

Electrophysiological evidence for conduction defect within the His bundle

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SUMMARY A change in the voltage and character of the His bundle deflection following premature atrial stimuli was observed and analysed in 5 of 95 patients having intracardiac conduction studies because of AV conduction disturbances. Of these 5 patients, 3 had spontaneous block within the His bundle, 2 of them showing block in other segments of the conduction system. With increasing prematurity of programmed atrial stimuli, there was a progressive decrease in the voltage of the His deflection, followed by a split His deflection, and finally disappearance of the His deflection. The voltage of the His deflection was also reduced in sinus beats following spontaneous His bundle premature beats. Similarly, during atrial stimulation at increasing rates, the His deflection decreased in voltage, split, and finally disappeared, but when Wenckebach periods appeared the His deflection reappeared in the first paced beat after the dropped beat. The preceding H-H interval was the only electrophysiological variable consistently related to the changes in the His deflection.

These changes in His deflection can be explained electrophysiologically as the result of a conduction disturbance within the His bundle. The clinical significance of the phenomenon is discussed. The occurrence of this phenomenon during a conduction study makes it difficult or even impossible to localise the AV block precisely.

His bundle recordings have proved useful in the localisation of atrioventricular conduction disturbances. By the use of this method intra-atrial, AV nodal, His bundle, and infra-His blocks can be differentiated. Conduction disturbances within the His bundle are recognised from the widening of the H deflection to more than 25 ms and from the split His phenomenon (Rosen *et al.*, 1971, 1972; Puech and Grolleau, 1972; Bharati *et al.*, 1974; Puech, 1975). Furthermore, block is likely to be located in the common bundle when the HV interval is prolonged with normal QRS configuration, since the coincidence of an identical conduction delay in the right bundle-branch and in the anterior and posterior divisions of the left bundle-branch is highly improbable (Touboul and Ibrahim, 1972).

We present here 5 cases in which a decrease in amplitude, splitting, and disappearance of the His deflection, with increasing prematurity of the atrial extrastimulus, provided evidence for His bundle conduction disturbances.

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Methods

Intracardiac and His bundle electrograms were obtained by the usual method first described by Scherlag *et al.* (1969) and Damato *et al.* (1969). Under fluoroscopy a tri- or quadripolar catheter with interelectrode distances of 10 mm was introduced via the femoral vein across the tricuspid valve to record the His bundle deflection. In addition to electrographic and fluoroscopic control, correct positioning of the catheter was validated by local His bundle stimulation as described by Narula and Samet (1969) and Narula (1975a). The A and V deflections in this tracing were regarded as originating in the low right atrium and right ventricle, respectively. One or two additional tri- and quadripolar electrocatheters were placed for recording and pacing in the high right atrial position (in the vicinity of the sinus node) via the same femoral and/or the antecubital vein. In some cases the His bundle deflection was simultaneously recorded by two different electrocatheters. Simultaneously with 3 surface electrocardiographic leads, filtered bipolar intracardiac electrograms were recorded with paper speeds of 50, 100, and 250 mm/s (filter specification: high cutoff 400 Hz, low cutoff adjustable between 0·2 and 100 Hz, db: 18). Atrial stimuli were delivered in the high right atrial region using impulses of 0·3 to 0·5 ms in duration and twice diastolic threshold value. Stimulation rate was increased progressively with increments of 10/min. For programmed premature stimulation, single stimuli were given after every eighth spontaneous beat, starting in the atrial refractory period and progressively increasing the A-St interval by 10 ms steps until the basic A-A interval was reached, after which the programmed stimulation was repeated in the opposite direction.

Hellige devices were used for amplifying, filtering, and recording, and a Biomedix diagnostic pulse generator was employed for stimulation.

Patients

During the 6 months of this study, His bundle recordings were obtained in 95 patients. Sixty-three of these had spontaneous conduction disturbances recognised on surface electrocardiograph leads; in 2 additional patients, first degree block (intra-atrial in one and His bundle block in the other) could be shown by intracardiac recording. Among these were 3 patients with overt signs of His bundle block and 2 patients with left bundle-branch block and prolongation of HV interval, who showed a progressive decrease in amplitude, splitting, and disappearance of the His bundle deflection with increased prematurity of the programmed atrial extrastimulus.

Results

CASE 1

This 40-year-old man was referred for His bundle recording because of short runs of tachycardia, occurring mostly during exercise, for the past year. He had had no previous heart disease. His resting heart rate was 64/min and on an exercise test heart rate did not exceed 115/min at 200 watts. After exercise he had frequent ventricular and atrial premature contractions, and then a short run of junctional tachycardia at a rate of 144/min. Intracardiac conduction intervals were A-A 55 ms, A-H 78 ms, H-V 40 ms, H deflection 28 ms. During His bundle recording, junctional tachycardia could be repeatedly triggered and terminated with single atrial stimuli. In this particular patient with evidence of first degree His bundle block (widening of H), the His deflection decreased in amplitude, split, and disappeared with increasing prematurity of the atrial extrastimulus during programmed stimulation. In addition to the disappearance of the His deflection, aberrant conduction (LBBB pattern) appeared when the A-St interval was 380 ms or less (Fig. 1). Sinus beats following interpolated supraventricular premature contractions with retrograde sinoatrial block also showed a decrease in amplitude or disappearance of the His deflection. Before extrastimuli were sufficiently early to cause AV block, the His deflection had already vanished; while this made it impossible to localise the block accurately, it seems likely that this was within the bundle of His.

CASE 2

This 51-year-old man was admitted complaining of ill-defined chest pain and with right bundle-branch block of recent onset. The latter was discovered when he was examined on account of weakness after a long ski run 4 months before admission. The resting electrocardiogram showed regular sinus rhythm at a rate of 72/min with a PR interval of 160 ms, complete right bundle-branch block, and a broad Q wave in leads III and aVF indicative of an old inferior scar.

In addition to right bundle-branch block, the His bundle recording showed a prolonged H-V interval indicating a conduction disturbance within the specialised ventricular conduction system.

Atrial pacing with the extrastimulus method showed a progressive H wave voltage decrease which occurred at 600 ms A-St interval and disappearance of the H deflection at an A-St interval of 490 ms. Finally AV block appeared at an A-St interval of 390 ms.

With rapid high right atrial stimulation the H deflection disappeared at a rate of 140/min. Long Wenckebach periods occurred at an atrial rate of 160/min. During Wenckebach periods, the H deflection reappeared regularly in the first beat after the dropped beat, thereby making it possible to localise the Wenckebach block in the AV node (Fig. 2). The H deflection reappeared consistently at an atrial stimulation rate of 180/min with 2:1 AV nodal block. A short run of junctional tachycardia was also recorded on the intracardiac electrogram.

CASE 3

This 69-year-old woman was studied because of increasing dizziness, a short period of faintness, and atypical chest pain, in May 1976. An electrocardiogram showed sinus rhythm with a rate of 58/min, left bundle-branch block, and a long PR interval (280 ms).

The intracardiac conduction study localised the first degree AV block below the His bundle, with HV interval 130 ms. In addition, there was a short

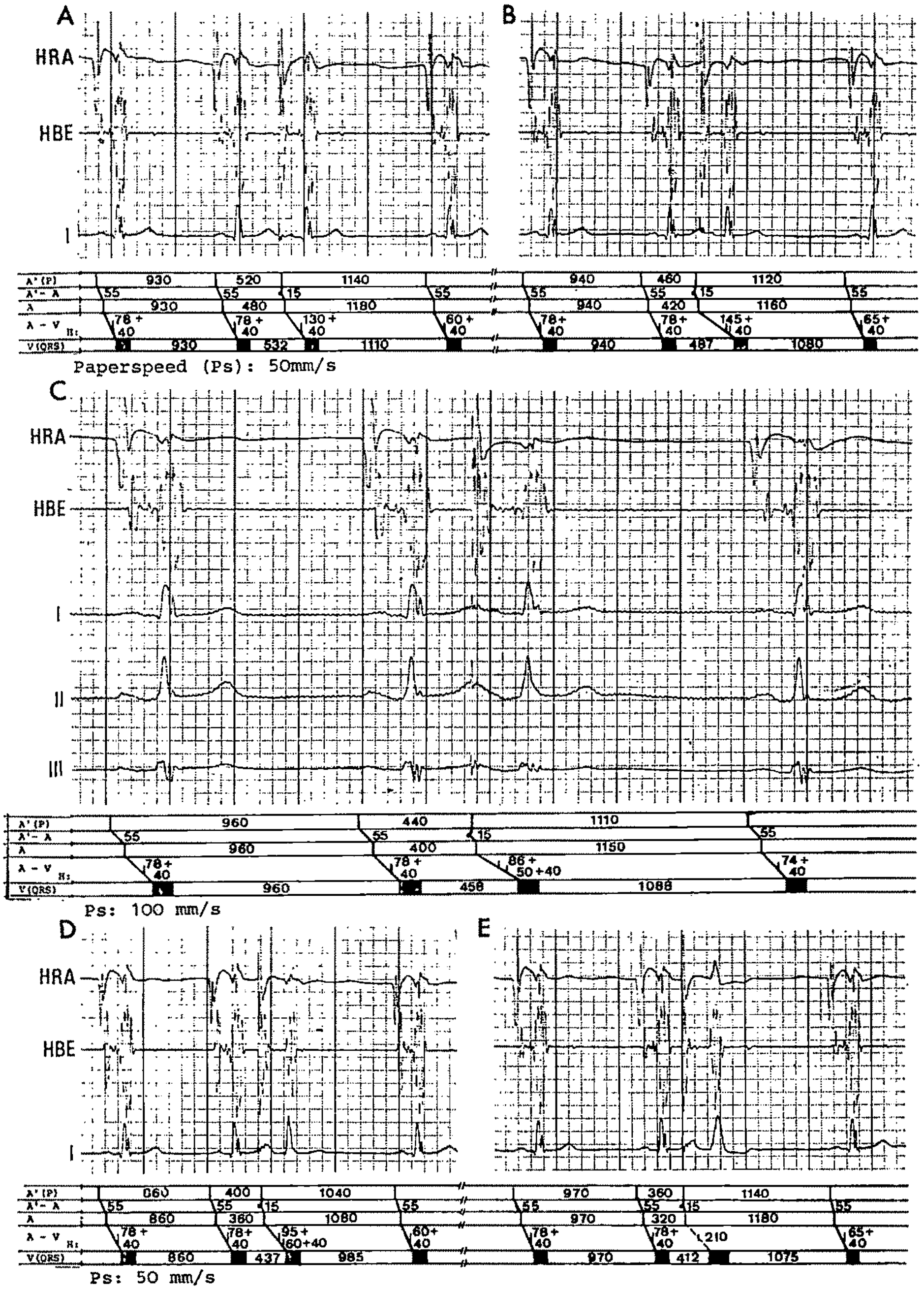

Fig. 1 *Case 1: Effect of premature atrial stimulation on voltage and character of His deflection in a patient with spontaneous His bundle block (H wave 28 ms). (A) No change of H deflection at a prematurity of 520 ms; (B) decrease in voltage of H deflection at a prematurity of 460 ms; (C) split His at a prematurity of 440 ms; (D) and (E) hardly recognisable H deflection probably with split at a prematurity of 400 and 360 ms, respectively. In E, LBBB pattern is seen.*

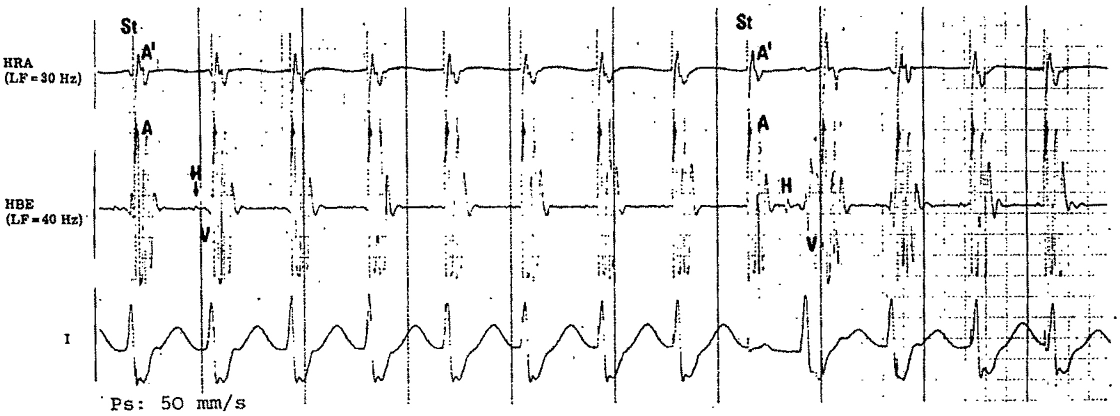

Fig. 2 *Case 2: The His deflection disappears during atrial pacing at a rate of 160/min. The atrial stimulation with accelerated rate also provokes long Wenckebach periods in the AV node. Following the dropped beat the His deflection reappears in the first beat of the succeeding Wenckebach period.*

run of third degree infra-His block during the His bundle recording. During programmed stimulation there was a progressive decrease in amplitude of H deflection as the A-St interval was reduced from 560 to 430 ms. At 430 ms a split H appeared and was recognisable until the A-St interval reached 380 ms. At shorter A-St intervals (as in case 1) there were only indirect signs of AV conduction, viz A was followed by V without any recognisable deflection between the atrial and ventricular deflections until

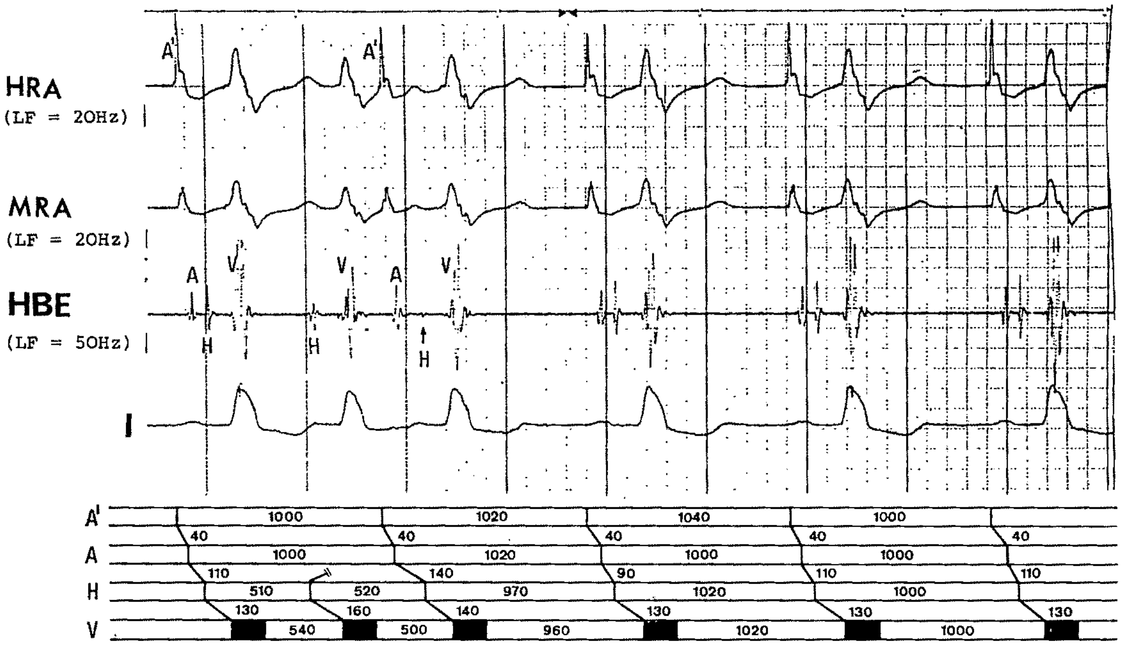

Fig. 3 *Case 3: Trifascicular block: left bundle-branch block with HV interval prolongation. The second beat is a His bundle premature beat which does not disturb the normal sinus rhythm. The His bundle deflection decreases significantly in the succeeding normal sinus beat (3rd beat) as a sign of block within the His bundle.*

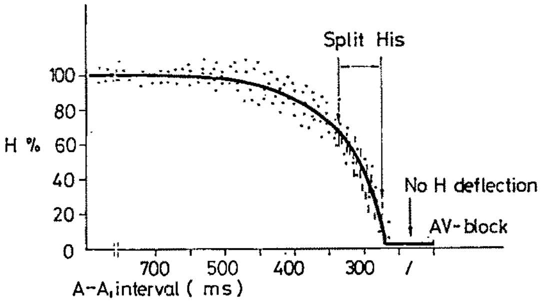

Fig. 4 *Case 3: Correlation between the prematurity of atrial stimulation and voltage of His deflection of atrial premature contractions expressed as percentage of the His deflection voltage of the preceding and succeeding beats (128 observations). Vertical lines denote split His deflections.*

a block occurred between A and V at A-St interval 320 ms. On asynchronous atrial stimulation at an accelerated rate of 130/min, Wenckebach periods occurred within the AV node. As in case 2, no H deflection was visible from the second beat of the Wenckebach period, but in the first beat following the dropped beat the H deflection reappeared, then disappearing again until the first beat after the next dropped beat. On atrial pacing at a rate of 154/min 2:1 AV block developed. This AV nodal block protected the bundle of His from impulses at the high atrial rate and the H deflection reappeared.

In this particular case we also saw several premature beats originating in the His bundle, which were conducted to the ventricles without change in the QRS configuration, but blocked in retrograde direction by concealed conduction within the AV node. These premature His beats shortened the H-H interval preceding the next normal sinus beats which always showed an H deflection with decreased voltage (Fig. 3). By measuring the voltage of the H deflection in 128 cycles and expressing this as a percentage of the voltage of the H deflections of the preceding and following beats, the curve shown in Fig. 4 was obtained. This case was interpreted as showing first degree block in the bundle of His, a constant first degree and intermittent third degree block in the right bundle-branch in the presence of left bundle-branch block, that is trifascicular block. The patient had a pacemaker implanted and has been free from symptoms since that time.

CASE 4

This 66-year-old woman was admitted for a His bundle study because of a history of paroxysmal tachyarrhythmias over an 8 to 9 year period. The onset was insidious and over the preceding 6 months her attacks of tachycardia had become more frequent.

The resting electrocardiogram showed regular sinus rhythm at a rate of 75/min with PQ 195 ms,

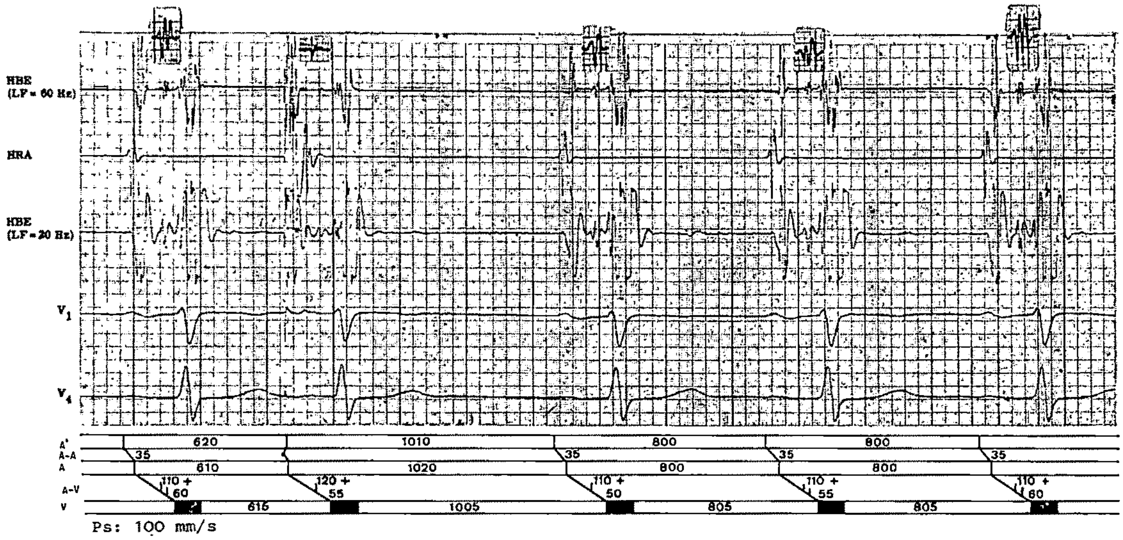

Fig. 5 *Case 4: Closely split His deflection during normal sinus rhythm (1st beat). The second beat is a stimulated atrial premature contraction in which the amplitude of the H deflection significantly decreases. Thereafter the compensatory pause gives time for a more effective recovery in the His bundle and its deflection becomes normal in the third beat. In the fourth and fifth beats the split His deflection progressively redevelops.*

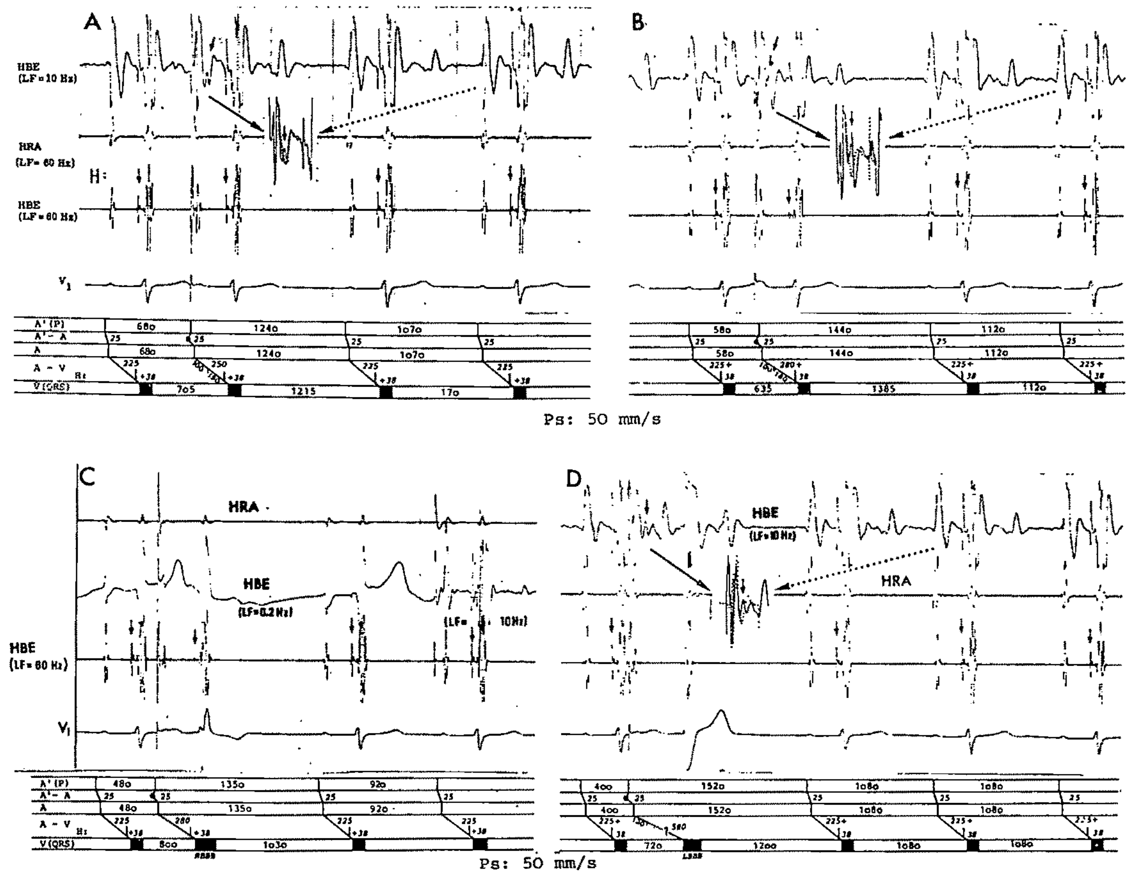

Fig. 6 *Case 5: With increasing prematurity of the stimulated atrial contraction the His deflection progressively diminished (B, C, D). As a sign of inhomogeneous conduction in the common bundle, first right bundle-branch block pattern (C), thereafter left bundle-branch block pattern (D) appears. Analysing the HBE lead with low cutoff of 10 Hz an additional deflection can be seen between the A and H deflections (arrow) in the stimulated atrial beats. See Fig. 7 and text for further discussion.*

QRS 80 ms, and QT 380 ms; there were minimal non-specific ST-T changes. Intracardiac conduction intervals were A′-A 35 ms, A-H 110 ms, and H-V 50 ms. The H deflection showed the split H phenomenon and was 34 ms in duration.

During atrial stimulation with single stimulus method, the H deflection decreased in voltage and disappeared with increasing prematurity. At and below an A-St interval of 480 ms atrial stimuli were conducted with left bundle-branch block. On the other hand, we often observed that the split His phenomenon disappeared following the compensatory pause after the premature stimulation, and His deflection becoming normal in form and duration for that single beat (Fig. 5). Again the voltage of the His deflection showed a direct relation to the length of the preceding H-H interval both during rapid atrial stimulation and with the extrastimulus method. The effect of a single atrial stimulus with A-St interval of 325 ms was to cause runs of junctional tachycardia, which could be terminated with the double stimulus method. This case was interpreted as showing reciprocating junctional tachycardia in the presence of His bundle block, where the left bundle-branch block pattern was probably caused by the inhomogeneous conduction within the His bundle.

CASE 5

This 46-year-old woman was admitted for His bundle electrogram because of a 4-year history of bouts of tachycardia, vertigo, and syncope on getting up in the morning. Her symptoms had increased slowly in intensity over the years. The

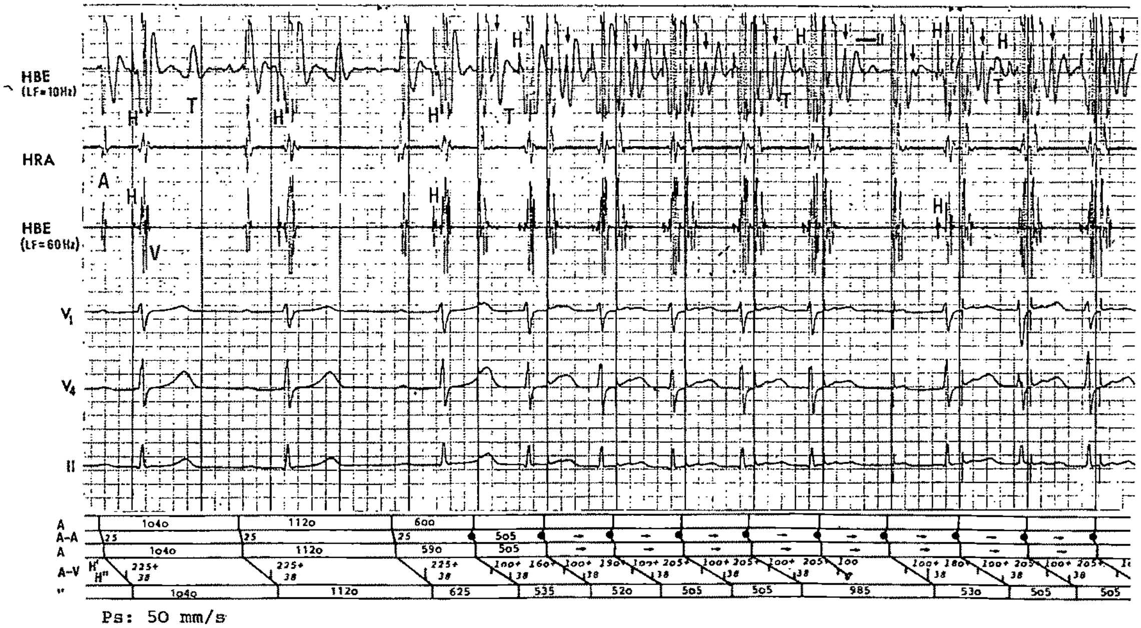

Fig. 7 *Case 5: A long period of second degree AV block develops during atrial stimulation at a rate of 118/min. The H deflection decreases during atrial stimulation and increases after the dropped beat in the conventional HBE lead. In another HBE lead with low electric cutoff an additional deflection (↓) appears 100 ms after the stimulated A. The progressive prolongation of PR and ↓-H intervals in the first two paced beats (4th and 5th beats) can be explained by the prematurity of the stimuli. Conduction in the next 3 beats is unchanged, suggesting that the block appearing after the additional deflection seen only in stimulated beats should be regarded as a Mobitz type II block within the His bundle. This deflection (↓) should not be regarded as the first component of split His deflection as its unchanging distance from the preceding A wave makes this interpretation improbable.*

resting electrocardiogram showed sinus rhythm at a rate of 56/min with first degree AV block (PR 290 ms, QRS 80 ms, QT 420 ms). The QRS axis was +30° and QRS configuration within normal limits. Intracardiac conduction intervals were A′-A 25 ms, A-H 225 ms, and H-V 38 ms. The duration of the H deflection was 28 ms.

On the resting electrocardiogram there were episodes of SA block with junctional escape beats giving rise to an irregular rhythm. Sinus node recovery time was measured 8 times during the His bundle recording, the maximal prolongation being 4220 ms after rapid atrial stimulation at 150/min for 120 s. On 4 occasions sinus arrest followed rapid atrial stimulation and a junctional escape rhythm took over with an escape interval of 1800 ms and a rate of 44/min. On another occasion, sinus arrest was associated with a ventricular escape rhythm at a rate of 32/min which appeared 2400 ms after cessation of atrial stimulation. With programmed atrial stimulation the His deflection was the same as in sinus rhythm at an A-St interval 660 ms. However, with A-St interval 560 ms the H deflection became smaller and wider but conduction into the ventricle remained normal. At 450 ms the H deflection was barely discernible and conduction took place only through the left bundle-branch (right bundle-branch block pattern). At A-St intervals of 450 and 400 ms the H deflection decreased further and disappeared, respectively, and conduction then was only through the right bundle (left bundle-branch block pattern) (Fig. 6). Atrial pacing at a rate of 120/min provoked periods of second degree AV block. Here again the His deflection became smaller and then increased to its former amplitude following the dropped beats of the Wenckebach periods in the His bundle recording with filter set for 60 Hz low cutoff. In this particular case, the His recording with filter set for 10 Hz low cutoff showed an additional deflection at high rates and during premature atrial stimulation. Its distance from the preceding A wave was shorter than the A-H interval in sinus rhythm and did not change with either prematurity or rate of stimulation (Figs 6 and 7). Block causing the dropped beat of the Wenckebach periods occurred between this low rising deflection and the His deflection (Fig. 7).

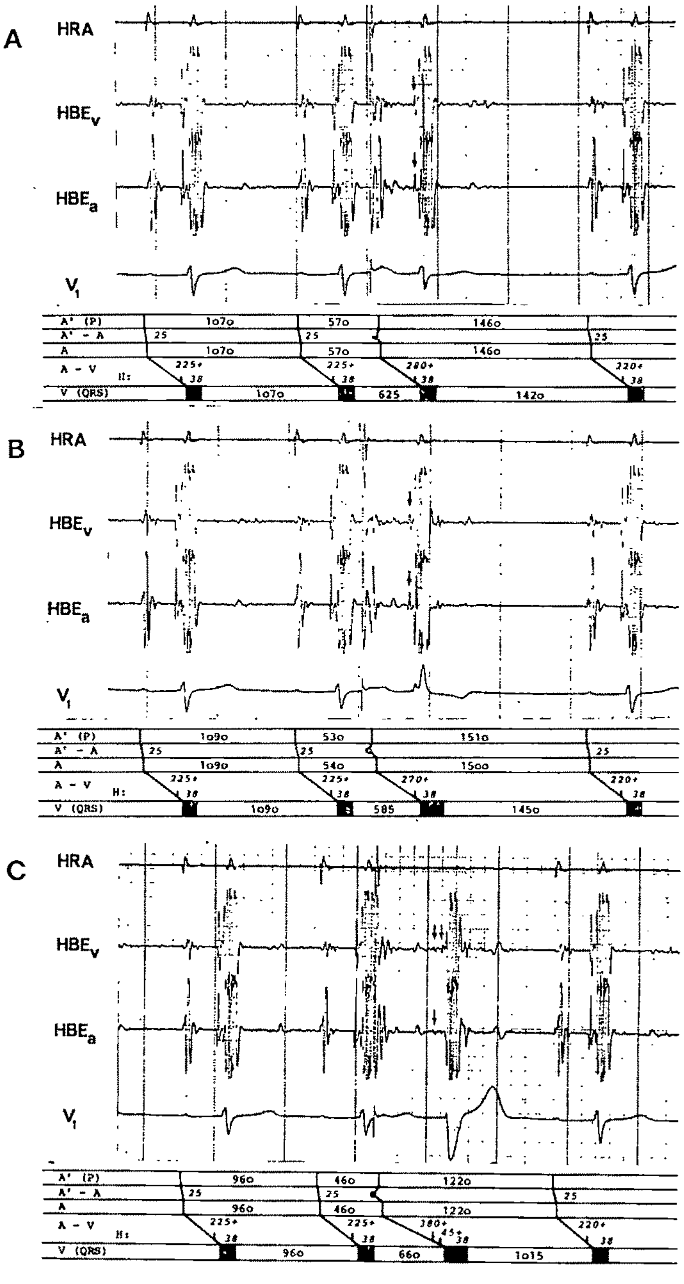

Fig. 8 *Case 5: With premature stimulation, the His deflection changes in identical fashion in each of the two simultaneous bipolar His bundle electrograms (HBE) which were recorded by the two distal (ventricular HBE, HBEv) and two proximal (atrial HBE, HBEa) poles of a quadripolar catheter. Note the difference in voltage of A in the two tracings. With premature stimulation at 460 ms a split His occurs (C); the distal H deflection is clearly recognisable only in HBEv. Arrows show His deflection in stimulated beats.*

Discussion

Accepted as criteria for block within the His bundle are widening of the His deflection, its duplication (split H), and first, second, or third degree blocks below the H deflection with narrow QRS configuration (Rosen *et al.*, 1971, 1972; Puech and Grolleau, 1972; Touboul and Ibrahim, 1972; Bharati *et al.*, 1974). Block in the bundle of His is commonly associated with conduction disturbances at other levels in the conduction system. Puech (1975) reported on 383 cases of spontaneous AV block. His bundle involvement was present in 68 cases. In 22 of these 68 patients (32%) His bundle block was associated with conduction disturbances below the His bundle (wide QRS). On the other hand 13 per cent of his 173 cases of intraventricular conduction disturbance showed additional His bundle block. In 72 per cent of Narula's (1975b) 122 cases of first degree AV block delayed conduction occurred in multiple segments of the AV conduction system. These studies indicate that in case of AV block, involvement of more than one segment of the conducting system is common.

In 4 of our 5 cases spontaneous conduction disturbances were present, and in 3 cases the His bundle electrogram showed first degree block within the common bundle.

During premature stimulation a decrease of voltage, a duplication, and finally disappearance of the His deflection were observed, this phenomenon being repeatedly reproducible in these patients. Because of the method of His bundle electrography, any change in the amplitude and shape of the His bundle deflection has to be carefully interpreted. In the opinion of Narula (1975a) these changes should not be taken to indicate an alteration of conduction in the His bundle. He attributed reduction in amplitude of the H deflection with premature atrial stimulation to dislocation of the catheter by anomalous atrial contraction. But if the premature stimulation shown in his figure was able to dislocate the recording electrode, we must conclude that the following sinus beat restored it to its previous position. We could accept this explanation for a decrease or disappearance of the His potential in single instances, but generally our experience does not confirm this view as we have always seen fluctuating changes in the His deflection when caused by electrode movement. In our reported cases the change of voltage of the His deflection always took place suddenly and was a function of the preceding H-H interval, which was unrelated to the site of origin of the beats showing this change. The amplitude of the His bundle deflection decreased progressively with the shortening of the A-St interval during programmed stimulation. Furthermore disappearance of the H deflection was preceded in 3 of these 5 patients by its splitting (Figs. 1 and 8). A change in the site of origin of the atrial contraction had no effect on the His deflection; thus, the same His deflection was present during atrial stimulation and normal sinus rhythm. When premature stimuli were delivered during the paced rhythm, the decrease in size of the H deflection was the same as in the premature beats in sinus rhythm. A diminution of the H deflection was also seen in sinus beats if they came early following stimulated or spontaneous atrial or His bundle deflections, as in Fig. 3. When two separate His bundle recordings were obtained using adjacent poles of a multipolar catheter, changes in the voltage of the His deflection were identical in the two tracings (Fig. 8). The presence of frequent His bundle premature beats and junctional tachycardias in our cases are additional evidence for a lesion in the common bundle, as has been emphasised by others (Puech and Grolleau, 1972; Narula, 1973). At a stimulation rate provoking Wenckebach periods in the AV node, rate, origin, and pattern of atrial contraction remain constant, but as shown in Fig. 2 this rate caused the disappearance of the H deflection, which reappeared again in the first beat following the dropped His-Purkinje deflection. At a higher atrial stimulation rate with 2:1 AV block, His bundle deflections reappeared at a slower rate below the block, proving that its presence does not depend on rate and pattern of atrial contraction but on the time available for repolarisation of the common bundle. Illustrations showing the same phenomenon of decrease in amplitude of the His deflection during premature atrial stimulation can be found in previous publications but, as far as we know, have not been interpreted as showing a conduction defect within the His bundle. Some examples are Figs. 4—2, 4—3, 6—6, and 6—16 in the recent book by Lister *et al.* (1976), three figures in Narula's book (1975c) (Chapter 10 Fig. 9, Chapter 14 Fig. 11b, and Chapter 14 Fig. 2). In the excellent Fig. 31 of Damato *et al.* (1975), the first premature stimulation was followed by a decrease in amplitude of the His deflection, by an extreme prolongation of H-V interval, and by a left bundle-branch block pattern. Following the second stimulation in the same figure, the His deflection is even smaller, the H-V prolongation is less, and the QRS complex shows a right bundle-branch block pattern, as in our case 5. In contrast to these findings, Fig. 4.32 of Puech (1975) showed, in a patient with left bundle-branch block, a sudden increase in voltage of His potential, shortening of the H-V interval, and disappearance of the left bundle-branch block for a single beat during a Wenckebach period. Puech noted this change in the His deflection in the legend to his figure, but did not explain it.

It is necessary to find an electrophysiological explanation for the inability to record a His deflection in atrial premature beats in these patients, especially as 4 of our 5 patients had manifest signs of conduction disturbance within the His bundle (widening of the H deflection, H-V prolongation with normal QRS, split H, and His bundle premature beats), accompanied in 3 cases by block in other segments of the conducting system.

An example of conduction without a detectable electrographic sign is the spread of an impulse in the AV node. The possibility that the N deflection arises in the AV node has been widely discussed (Hoffman *et al.*, 1960; Damato and Lau, 1969; Damato *et al.*, 1970; Massumi, 1970; Brodsky *et al.*, 1971; Mendez and Moe, 1972; Kupersmith *et al.*, 1973; Narula, 1973), but in agreement with most authors (Hoffman *et al.*, 1960; Mendez and Moe, 1972; Kupersmith *et al.*, 1973; Narula, 1973; Narula, 1975a) we believe that it originates not in the AV node but in intra-atrial tracts and label it Tr, as proposed by Narula. Some authors attribute the absence of an AV node deflection to potentials too small to be recorded. According to Hoffman *et al.* (1960), in tissues such as the AV node with slow rise of depolarisation (dv/dt), the extracellular potential difference between the electrodes will be too small to give rise to an electrographically recordable signal.

Hecht (1957), Vaughan Williams (1959), and Spach *et al.* (1972) have noted that extracellular potential of cardiac fibre resembles the second derivative of the rate of rise (phase 0) of action potential. This finding means that with decreasing the rise of phase 0 depolarisation highly decreases the extracellular electrographic sign of this process and also explains the lack of direct electrographic evidence of the impulse conduction in sinus and AV node.

Paes de Carvalho (1962) writes: 'Activity which spreads at 0·05 m/s and takes 30 ms to attain maximum depolarization at given spot is not likely to show up in extracellular recordings especially if the size of the electrodes or the frequency response of the apparatus are not in keeping with the slowness of the process.' This statement was confirmed by Kupersmith *et al.* (1973) who placed electrodes directly on the AV node in 58 patients during open heart surgery, but could not demonstrate any recognisable activity of the node. However, in their study only electric signals below 12 Hz were filtered out in contrast to the usual intracardiac electrographic technique using a low filter of 40 to 60 Hz. As it was possible that slowly rising His bundle depolarisations had been filtered out in our patients, we repeated the programmed stimulation in 4 cases (cases 2 to 5) filtering out simultaneously on one channel the signals below 60 Hz, on another decreasing progressively the filter level to 0·2 Hz. In 3 of the 4 cases we obtained no additional information by this technique, but in the last case an additional deflection appeared in the His bundle tracing in the stimulated atrial beats with low (10 Hz) filter cutoff (Figs. 6 and 7). Since this followed A by a fixed coupling interval it could be related to atrial depolarisation, though its exact origin was uncertain. A split His phenomenon cannot be excluded, and it also may reflect afterswing of the recorder unit due to electric resonance (see also legend to Fig. 7). The AV block during atrial stimulation at high rates was located between this slow rising potential and the His deflection (Fig. 7). During premature stimulation, the His potential disappeared in this lead before the AV block appeared (Fig. 6).

We suggest that in these cases conduction within the His bundle closely resembled that in the AV node, this electrographic similarity being the result of an electrophysiologic similarity. It is well known that premature impulses (spontaneous or paced) can meet a stage of incomplete repolarisation. The onset of an action potential at a lower level of membrane potential results in a slower phase 0 depolarisation and slower conduction velocity. These changes of membrane events will appear as prolongation of the conduction interval, concealed, and decremental conductions. This also means that in an extracellular recording there is only a quantitative difference between widening and disappearance of an electrographic deflection, in this case a His deflection. According to James (1976), the His deflection arises from the P cells of the bundle. In animal experiments, he produced an intermittently split H deflection, explaining the splitting by dissociation of P cells, and the reconnection of the two components of H by their 'regluing'. These experiments do not explain why tissues containing even more P cells do not show electrographic signs of depolarisation, but show that in cases with split H there is a silent zone between the upper and lower part of the common bundle.

Normally we cannot produce any recognisable change in His bundle conduction by atrial stimulation since the conduction quality of the common bundle is superior to that of the AV node, so that the latter functions as the 'physiological gate' to the whole AV conduction process. But, when conduction in the His bundle decreases to or below the level of that of the AV node by virtue of a change in its membrane potential and form of action potential, it will take over the role of the gate. Thus, a first degree block within the His bundle can be recognised either by the well-known signs of His bundle block or only by testing the bundle with premature and high frequency stimulation. Our clinical findings are supported by Myerburg *et al.* (1970) who described the progressive change of action potential along the His bundle and Purkinje system. Benitez *et al.* (1973) showed that this progressive increase in rate of rise of action potential along the His bundle can be abolished by inhibiting the fast inward current by a KCl solution of 29·3 mmol/l or by tetrodotoxin so that its action potential becomes similar to that of AV node. Their model experiments provide an electrophysiological explanation of our clinical observations which on the other hand support the sinoventricular conduction concept of Sherf and James (1969).

The clinical significance of our present findings is related to the localisation of AV blocks. Thus when an A deflection is not followed by H and V the block cannot always be localised in the AV node. The site of block is clear if both H and V, or V only, disappear suddenly with increased prematurity of the atrial stimulus. But if the disappearance of the H deflection is preceded by its progressive decrease in voltage, AV conduction is proven only indirectly by the fact that A is consistently followed by V. In such cases the supra-, intra-, or infra-Hisian localisation of the site of the AV block is impossible. Additional tests (rapid atrial pacing, direct His bundle pacing, recording the His bundle electrogram with different filtrations for detecting slow rising potentials, examination of retrograde conduction, etc.) have to be performed to determine the exact localisation of the AV conduction defect.

An unsuccessful attempt to record a His deflection is not necessarily a technical failure. It can also be a sign of His bundle block as was seen in an additional case of ours with intermittent bifascicular block and Adams-Stokes syncope. During the electrophysiological study we had difficulty in recording an H deflection, but this finally appeared in the form of a split H or a single H deflection of 40 ms duration for a few beats only and then disappeared again. Nevertheless we suggest that a diagnosis of His bundle block should be made on the basis of the absence of an H deflection only if its absence is proved conclusively by approaching the His bundle from different directions (superior or inferior vena cava, coronary sinus, aorta).

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Echocardiography in assessment of infants with complete d-transposition of great arteries

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SUMMARY Echocardiography was performed prospectively in 43 infants with complete d-transposition of the great arteries (d-transposition), 29 of whom were in the first week of life. When the final diagnosis had been established an assessment was made of the reliability of the echocardiographic findings and their contribution to the clinical diagnosis.

The atrioventricular valves were correctly assessed in 40 infants and incorrectly in 3, the error being important in 1. The ventricular septum was recorded in 42 and failure to record a normal septum occurred in 1. Abnormal great arterial root positions were recorded by echocardiography in 35 of 43 infants, but minor variations in position could not be detected with accuracy. Assessment of the root positions was incomplete in 7 of 43 and incorrect in 1.

The great aterial root positions were determined by cineangiocardiography and showed pronounced variation, as also occurs in connection disorders other than d-transposition. The connection diagnosis, therefore, cannot be established by the demonstration of any particular root positions.

Echocardiography made a significant contribution to the clinical diagnosis of d-transposition in 35 of 43 infants (81%), and the findings were incomplete in 5 of 43 (12%). Seriously misleading information was provided in 3 of 43 (7%).

Echocardiography aids management in the majority of infants with d-transposition and can help to exclude this condition in infants who are hypoxic from other causes.

Complete transposition of the great arteries is a potentially lethal condition and survival largely depends upon prompt diagnosis and treatment (Rowe and Vlad, 1973). The use of echocardiography in the recognition of transposition of the great arteries was first described by Gramiak *et al.* (1973), but since then there has been little objective information about its role in the management of this condition. Echocardiography can contribute to the clinical diagnosis in the majority of infants with transposition and this report describes our experience in a group of infants in whom echocardiography was performed prospectively.

The report is confined to patients with visceroatrial situs solitus, a concordant ventricular d-loop (right-sided right ventricle) and transposition of the great arteries (d-transposition). Transposition of the great arteries is present when the aorta arises solely or mainly from the morphologically right ventricle and the pulmonary artery solely or mainly from the morphologically left ventricle (Van Praagh *et al.*, 1971). Brief mention is made of related conditions.

Patients

Between July 1974 and February 1977 echocardiograms were obtained in an unselected group of 180 infants aged less than 6 months who were admitted to Green Lane Hospital with suspected heart disease. Forty-three were subsequently shown to have d-transposition and form the basis of this report.

The age ranged from 6 hours to 17 weeks and there were 29 infants under 1 week. Echocardiograms were done and analysed as soon as possible after admission before establishment of the final diagnosis. No baby received sedation but the assistance of a nurse was available in all cases.

The diagnosis of d-transposition was established in all patients by cardiac catheterisation and biplane cineangiocardiography. In most patients contrast

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injections were made in both ventricles, and oblique views were recorded, but additional injection sites and other views were used where necessary. In addition surgical confirmation of the diagnosis was subsequently available in 27 cases and necropsy in 8. Anatomical details are shown in Table 1.

The clinical diagnosis was made in each case before echocardiography by a cardiologist (usually J.M.N.) and this was based upon the history, physical examination, 12-lead scalar electrocardiogram, and chest *x*-ray films. All echocardiograms were recorded by one of the authors (usually N.M.B.). In the first 23 cases echocardiograms were recorded without knowledge of the initial clinical assessment and in the last 20 cases they were recorded knowing the clinical assessment. This difference did not appear to influence results. After cardiac catheterisation and cineangiocardiographic studies a retrospective assessment was made in each case to determine whether or not the echocardiographic findings had contributed to the original clinical diagnosis.

Method of echocardiography

Echocardiograms were made with an Ekoline 20 echocardiograph. A 0·5 in 2·25 MHz transducer focused to 10 cm was used in the first 13 cases and a 0·25 in 5·0 MHz non-focused transducer was used in the remainder. Permanent records were made with polaroid film in the first 23 cases and with 35 mm photographic film strip records in the last 20 cases. An electrocardiogram was recorded with the echocardiogram only in selected cases.

Table 1 *Anatomy in 43 infants with d-transposition of the great arteries*

Classification according to clinical presentation	*No. of infants*	*Associated cardiac anomalies**	
(1) Poor mixing	24	Interatrial communication	1
		Small PDA	10
		Small VSD	5
		Small VSD and PDA	8
(2) Free mixing	13	Large PDA	7
		Large VSD	6
(3) VSD and PS	4	Virtual pulmonary atresia	1
(4) Complex	2	VSD, CO Ao, and PDA	2

PDA, persistent ductus arteriosus; VSD, ventricular septal defect; PS, pulmonary stenosis; CO Ao, coarctation of aorta.

*Additional anomalies included cleft anterior mitral leaflet (1), single papillary muscle to mitral valve (1), partial anomalous pulmonary venous connection (2), pulmonary artery overriding the interventricular septum (2), aneurysm of the membranous septum (1), overriding tricuspid valve with underdevelopment of right ventricle and mitral valve (1), and hypoplastic aortic arch (1). Several other infants had probable minor anomalies of the left ventricular outflow and 2 developed significant subvalvar pulmonary stenosis some months after the study.

The echocardiographic examination of the intr cardiac structures was made using the techniqu reported for normal neonates by Solinger *et a* (1972). The tehnique for describing the orientatic of the great arterial roots at the level of the sem lunar valves followed the principles described b Gramiak *et al.* (1973). Routine attempts were mac to scan from the anterior and posterior walls of tl posterior great artery to the ventricular septu and anterior cusp of the left atrioventricular valv respectively.

When using polaroid film, the atrioventricul valves, ventricular septum, and arterial roots we classified as normal, abnormal, or absent, an abnormalities were described. When using phot graphic film strip records, measurements we made of the range of movement of the atriover tricular valves, the left ventricular dimension, an the dimension of the great arterial roots (at enc systole). Detailed measurements were not made the right ventricular dimension or of the thickne of the ventricular septum and posterior left ver tricular wall because it became apparent th detailed measurements frequently could not b repeated with confidence in sick infants withou sedation.

Results

INTRACARDIAC FINDINGS

The echocardiographic assessment of normal rigl and left atrioventricular valves was correct in 4 of 43 infants. In one an overriding right atri ventricular valve shown by cineangiocardiograpl was mistaken in the echocardiogram for a le atrioventricular valve and the hypoplastic le atrioventricular valve in this infant was not r corded. One left atrioventricular valve classified normal by echocardiography was found to have single papillary muscle and another was found have a cleft anterior leaflet; both were thought function normally on clinical, haemodynamic, an cineangiocardiographic grounds. A scan from tl left atrioventricular valve to the posterior wall of tl posterior great artery, indicating probable mitra pulmonary continuity, was obtained in 36 of the 4 infants, and this was supported by cineangiocardi graphy in all. This scan could not be achieved in tl other 7 infants but in only 3 of these was the cineangiocardiographic, surgical, or necropsy ev dence of true mitral-pulmonary discontinuity.

The ventricular septum was recorded in 42 of 4 infants and in all the septum moved posteriorly systole. However, echocardiography failed to dete the ventricular septum in 1 infant with simp d-transposition and intact ventricular septum, ar this was an unexplained technical error leading to the false echocardiographic diagnosis of single ventricle.

POSITIONS OF GREAT ARTERIAL ROOTS

Table 2 shows the assessment of the great arterial positions in 43 infants with d-transposition by both cineangiocardiography (usually right and left anterior oblique views) and echocardiography. Their positions by cineangiocardiography were most often right-anterior aorta and left-posterior pulmonary artery, but other arrangements occurred frequently.

The right-anterior and left-posterior root positions were usually demonstrated as such by echocardiography (Fig. 1). Incomplete assessment occurred in 1 because of uncertain orientation and in another because only the abnormal left-posterior root was recorded.

Anteroposterior positions were usually considered right-anterior and left-posterior by echocardiography. Thus the relative positions in a left-right direction were not accurate by echocardiography though the root positions appeared abnormal. Incomplete assessment occurred in 1 because only the abnormal posterior root was recorded and in another the root positions were incorrectly assessed as right-posterior and left-anterior.

Side-side positions were usually considered right-anterior and left-posterior by echocardiography or the leftward great artery was not recorded. The relative distances of the great arteries from the chest wall were, therefore, not accurately assessed but, where both roots were seen, their positions appeared definitely abnormal. Where only one great arterial root was identified (always right-anterior) its position appeared abnormal.

Left anterior and right-posterior root positions were assessed correctly by echocardiography in 1 infant (Fig. 2) and incompletely in another in whom the severely hypoplastic right-posterior pulmonary artery was not recorded.

Table 3 shows measurements derived from strip records of the arterial roots, left atrium, atrioventricular valves, and left ventricular dimension in 17 infants with d-transposition. The pulmonary artery was approximately equal in dimension to the aorta in 4 and larger in the remainder, and the atrioventricular valves were normal in all. No infant in this group had pulmonary stenosis. The report that d-transposition is probable when both semilunar valves are recorded simultaneously (Dillon *et al.*, 1973) was not supported (Fig. 3).

CONTRIBUTION OF ECHOCARDIOGRAPHY TO CLINICAL DIAGNOSIS

In Table 4 the contribution of echocardiography is shown in relation to the initial clinical diagnosis. Though d-transposition was the primary clinical diagnosis in almost half the cases, other diagnoses were entertained in the remainder, and in 6 the

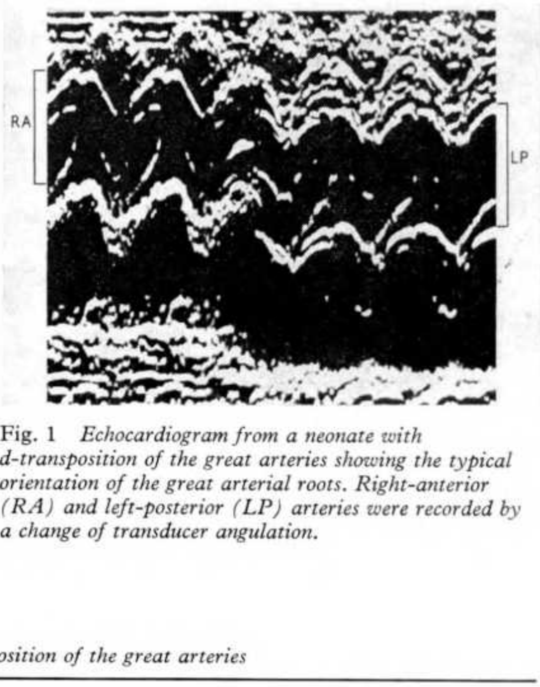

Fig. 1 *Echocardiogram from a neonate with d-transposition of the great arteries showing the typical orientation of the great arterial roots. Right-anterior (RA) and left-posterior (LP) arteries were recorded by a change of transducer angulation.*

Table 2 *Great arterial positions in 43 infants with d-transposition of the great arteries*

*Cineangiocardiography**		*Echocardiography* *RA, LP*	*AP*	*Side-side*	*LA, RP*	*Incomplete*	*Incorrect*
RA, LP	23 (53%)	21	—	—	—	2	—
AP	11 (26%)	8	1	—	—	1	1
Side-side	7 (16%)	3	—	1	—	3	—
LA, RP	2 (5%)	—	—	—	1	1	—

Note: 3 cases classified AP by cineangiocardiography were borderline RA, LP. 3 cases classified side-side by cineangiocardiography were borderline RA, LP.

*Usually right and left anterior oblique views.

RA, right-anterior; LP, left-posterior; AP, anteroposterior; LA, left-anterior; RP, right-posterior.

primary clinical diagnosis was pulmonary atresia with normally-related great arteries. In conjunction with clinical findings echocardiography strongly supported the diagnosis of d-transposition in 33 patients and an important clinical alternative (single ventricle) was excluded in another 2. On the other hand echocardiography was frankly misleading in 3 cases, in 1 because of incorrect assessment of the great arterial positions and in another because of failure to show the interventricular septum. The third case was complex with severe hypoplasia of the main pulmonary artery, an overriding tricuspid valve, and underdevelopment of the right ventricle and mitral valve. The atrioventricular valves were incorrectly assessed and the arterial roots incompletely assessed in this infant. Echocardiographic

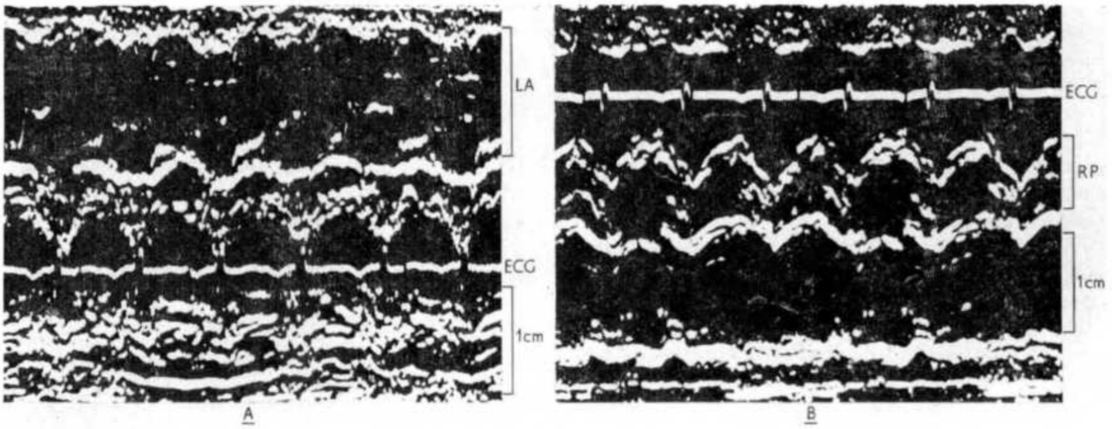

Fig. 2 *Echocardiograms from a neonate with d-transposition of the great arteries and atypical orientation of the great arterial roots. Clinical signs suggested a complex lesion, with radiological evidence of reduced lung blood flow. (a) Record shows a left-anterior (LA) arterial root of normal dimension (13 mm). (b) Record shows an abnormal right-posterior (RP) arterial root of reduced dimension (7 mm). These findings were compatible with abnormally-positioned great arteries (see text).*

Table 3 *Echo dimensions from strip records of great arterial roots, left atrium, atrioventricular valves, and left ventricle in 17 infants with d-transposition of the great arteries*

Infant No.	*Age (d)*	*Wt (kg)*	*VSD*	*Other lesion*	*Great arterial root positions*		*Aorta (mm)*	*Pulmonary artery (mm)*	*Left atrium (mm)*	*Right AV valve—range (mm)*	*Left AV valve—range (mm)*	*Left ventricle (mm)*
					Echo	*Angio*						
1	3	3·2	—	Mod. PDA	RA, LP	RA, LP	10·8	12·5	13·3	14·5	11·1	19·5
2	1	3·6	—	Small PDA	RA, LP	AP	12·2	12·4	13·0	12·3	11·8	16·6
3	12	3·2	—	Large PDA	side-side	side-side	11·7	14·5	—	12·4	11·3	24·6
4	2	2·5	Small	Small PDA	RA, LP	RA, LP	12·5	12·2	8·8	11·6	9·8	18·5
5	2	3·9	—	Small PDA	RA, LP	RA, LP	11·9	13·0	12·0	14·6	10·6	20·5
6	1	3·9	Small	Small PDA	RA, LP	AP	10·4	12·3	13·9	10·0	10·3	18·6
7	2	2·7	—	Large PDA	AP	AP	10·9	13·0	10·5	8·5	8·8	20·8
8	77	4·1	Mod.	CO Ao, large PDA and overriding PA	RA, LP	side-side	9·3	12·8	17·4	15·7	13·0	25·4
9	3	3·3	Small	Small PDA	RA, LP	AP	12·1	12·6	15·3	13·1	10·5	20·0
10	1	3·3	—	Mod. PDA	RA, LP	RA, LP	11·5	13·6	15·2	13·0	10·4	21·3
11	4	3·1	Mod.	—	RA, LP	RA, LP	12·1	14·6	13·6	11·8	10·3	22·1
12	1	3·1	—	Mod. PDA	RA, LP	RA, LP	10·4	11·5	13·4	11·2	9·7	16·3
13	4	3·6	Small	—	RA, LP	RA, LP	11·7	11·9	11·5	11·1	9·3	22·8
14	8	2·5	Small	Small PDA	RA, LP	AP	10·0	12·0	11·7	13·1	10·1	18·6
15	1	3·9	Small	Small PDA	RA, LP	AP	11·1	11·1	8·1	12·1	9·3	15·9
16	7	3·4	—	Small PDA	RA, LP	RA, LP	11·1	14·1	13·2	11·0	9·5	21·1
17	35	3·6	Small	Small PDA	RA, LP	RA, LP	10·6	14·6	14·4	12·8	12·1	29·6

VSD, ventricular septal defect; Echo, by echocardiography; Angio, by cineangiocardiography; AV, atrioventricular; PDA, persistent ductus arteriosus; RA, right-anterior; LP, left-posterior; AP, anteroposterior; CO Ao, coarctation of aorta; PA, pulmonary artery.

findings were incomplete in another 5 infants because only 1 of 2 abnormal arterial roots was shown.

Thus echocardiography made a significant contribution to diagnosis in 81 per cent of cases, 78 per cent in the first half of the study using polaroid film for recording and 85 per cent in the latter half using photographic film strip recordings. We attribute the improved results mainly to greater experience, as they did not seem much influenced by knowledge of the clinical assessment and the use of photographic strip records in the later part of the study.

OTHER DIAGNOSES

There were 12 additional infants in whom the diagnosis of d-transposition was entertained clinically but in whom echocardiography showed the great arterial positions to be normal (Fig. 4 and 5). Four of these infants were hypoxic from non-cardiac causes and required no further cardiac studies. In the remainder subsequent investigation excluded d-transposition and showed other complex cardiac anomalies, great arterial positions being normal in all.

There were another 6 infants whose great arteries were assessed by echocardiography as right-

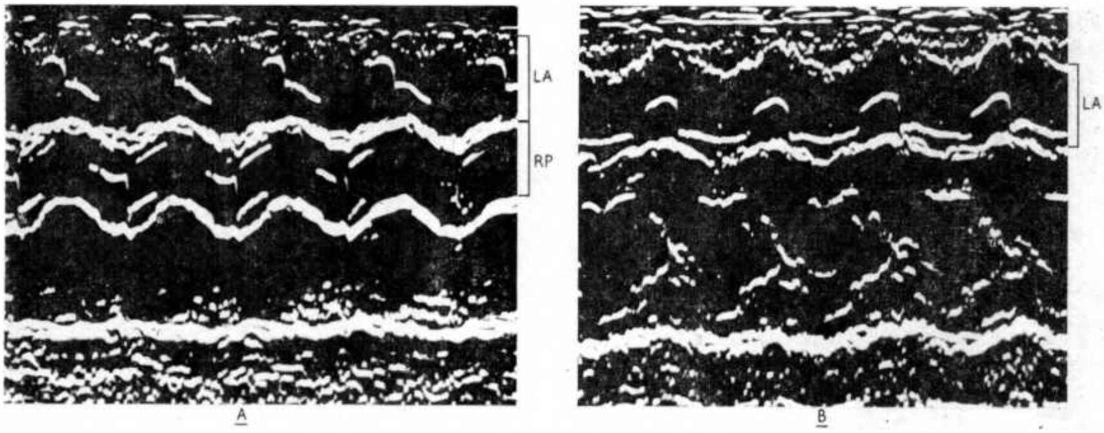

Fig. 3 *Echocardiograms from a neonate with a persistent ductus arteriosus and normally-related great arteries. (a) Simultaneous recording of semilunar cusps of both the left-anterior (LA) and right-posterior (RP) arteries. Note that the anterior wall of the left anterior artery is not recorded. (b) Correct transducer angulation allows better recording of the LA artery only.*

Table 4 *Assessment of contribution of echocardiography to clinical diagnosis in 43 infants with d-transposition of the great arteries*

Clinical diagnosis	*No. of infants*	*Echocardiographic contribution*			
		TGA supported	*Important alternative excluded*	*Echo incomplete*	*Echo misleading*
(A) TGA probable	*21*	18	—	2	1
TGA only diagnosis	14				(IV septum not recorded)
TGA most likely diagnosis	7				
(B) TGA possible	*16*	11	2	2	1
TGA equal alternative diagnosis	10				(Arterial roots misinterpreted)
TGA secondary diagnosis	6				
(C) TGA unlikely	*6*	4	—		1
(clinical diagnosis pulmonary atresia)					(AV valves and arterial roots inadequately demonstrated)

Group A includes: 14 poor mixing, 6 free mixing, and 1 complex case.
Group B includes: 7 poor mixing, 6 free mixing, 2 VSD and PS, and 1 complex case.
Group C includes: 3 poor mixing, 1 free mixing, and 2 VSD and PS.
TGA, transposition of the great arteries; IV, interventricular; AV, atrioventricular; VSD, ventricular septal defect; PS, pulmonary stenosis.

anterior and left-posterior but who did not have d-transposition. In 3 of these the assessment was correct (2 with situs inversus and concordant l-transposition and one with double-outlet right ventricle). In the other 3, all with complex anomalies, the echocardiographic assessment was incorrect.

Discussion

Our approach to the use and evaluation of echocardiography differs from that used in previous reports. Believing that the reliability of echocardiographic observations could not be judged impartially in patients with a known diagnosis, the echocardiograms were performed without knowing the final diagnosis. We have, therefore, attempted an unbiased evaluation of echocardiography done prospectively. We do not think that knowledge of the initial clinical assessment at the time of echocardiography in 20 infants affected this approach.

The use of single-transducer echocardiography in the assessment of d-transposition illustrates both the advantages and limitations of this technique. While it is excellent in displaying much of the intracardiac anatomy, it has limitations in displaying the ventriculoarterial connections on which the diagnosis of d-transposition should be based (Brandt and Calder, 1977).

With 2 exceptions the atrioventricular valves and interventricular septum were satisfactorily displayed by echocardiography. Atrioventricular valve anatomy was misinterpreted in 1 infant with an overriding tricuspid and a hypoplastic mitral valve, and the interventricular septum was not shown satisfactorily (even in retrospect) in another.

In the normal heart the aorta is right sided and posterior and the pulmonary artery is leftwards and anterior. The method of displaying abnormal

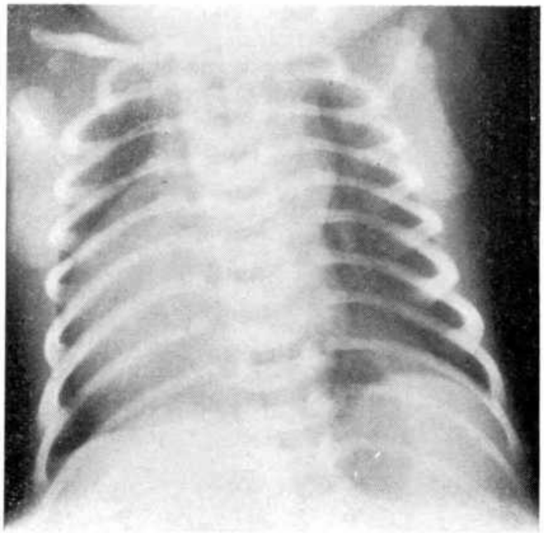

Fig. 4 *Chest* x-*ray film of a mildly cyanosed 8-day-old infant in whom a complex anomaly, including d-transposition, was suspected. Film shows isolated dextrocardia. This was associated with an anterior diaphragmatic hernia.*

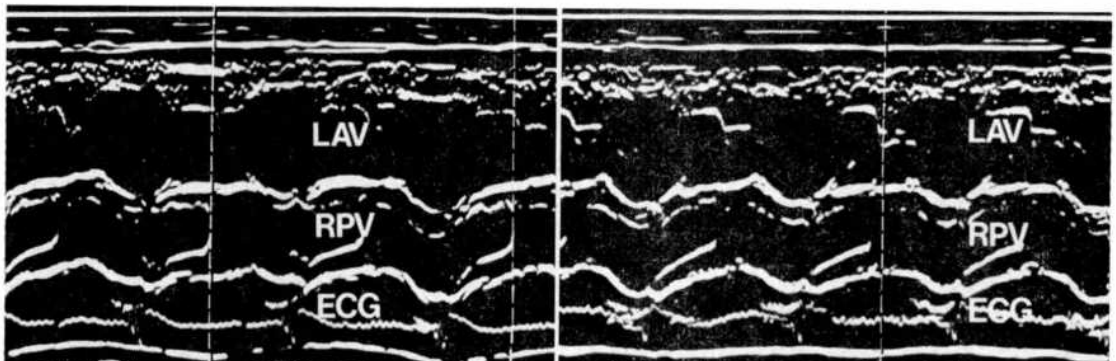

Fig. 5 *Echocardiograms showing the timing of semilunar cusp closure in the infant whose chest* x-*ray film is shown in Fig. 4. The vertical interrupted lines indicate the timing of closure of the semilunar cusps. (a) QRS closure time of the right-posterior semilunar valve (RPV) is 215 ms. (b) QRS closure time of the left-anterior semilunar valve (LAV) is 226 ms. These findings strongly support normally related great arteries (see text).*

arterial roots in d-transposition (Gramiak *et al.*, 1973) relies upon the presence of the typical abnormal arrangement, a right-anterior aorta and left-posterior pulmonary artery (Fig. 1). However, previous studies using anteroposterior and lateral angiocardiography have shown this arrangement in only 69 per cent (Carr *et al.*, 1968), and in 50 per cent of cases (Guerin *et al.*, 1970). Similar findings occurred in the present study and the typical positions were shown by biplane cineangiocardiography with oblique views in 23 of 43 (53%) infants with d-transposition. The classification of arterial positions can be somewhat arbitrary; the root positions in 6 cases classified either anteroposterior or side-side by cineangiocardiography were borderline right-anterior and left-posterior. The remaining cases showed pronounced variation in the relative positions of the great arterial roots, and it is obvious that the diagnosis of d-transposition cannot be made on the basis of these positions alone. Furthermore, though the finding of right-anterior and left-posterior arterial roots in an infant is strongly suggestive of d-transposition, it cannot be considered diagnostic by itself as this arrangement occurs in other conditions.

Abnormal arterial positions can be shown by echocardiography in most infants with d-transposition. The echocardiographic demonstration of right-anterior and left-posterior arterial roots supports a clinical diagnosis of d-transposition, though in some cases the actual positions may be anteroposterior and in others side-side. This difficulty in establishing the true relation of the root positions is presumably because of minor variations in transducer placement.

We regard the demonstration of right-anterior and left-posterior arterial roots, with the posterior wall of the posterior root continuous with the left atrioventricular valve on scanning, as strong supportive evidence for d-transposition. Because of variations in cardiac position, and in the development and rotation of the subaortic and subpulmonary coni, the echocardiographic identification of abnormal arterial root positions does not establish the connections of d-transposition, but in conjunction with other data it makes it probable. The echocardiographic findings must, therefore, be taken in conjunction with the clinical findings in d-transportion and, in this situation, our study has shown that echocardiography can provide additional information in at least 80 per cent of infants with this condition.

Echocardiography can still be useful when the positions of the great arterial roots are atypical. Fig. 2 shows the echocardiograms of a 3-day old infant with clinical signs suggesting a complex lesion and with evidence of reduced lung blood flow in the chest *x*-ray film. Echocardiography showed a normal-sized left-anterior arterial root and a right-posterior root of about two-thirds normal size, with the posterior wall of the posterior root in continuity with the left atrioventricular valve. In conjunction with the clinical and chest radiographic findings it could be deduced that the larger left-anterior root was likely to be the aorta, and that transposition or malposition of the great arteries was present. The final diagnosis was d-transposition with the left-anterior aorta arising from the right ventricle and the small right-posterior pulmonary artery arising from the left ventricle. As expected pulmonary stenosis was also present.

In passing it is of interest to note that we have examined 2 infants with situs inversus and concordant l-transposition (the equivalent of d-transposition in situs solitus) in whom the great arterial roots were in a right-anterior and left-posterior position, not left-anterior and right-posterior as one might expect. We have also examined 2 infants with situs solitus and discordant l-transposition. In 1 the great arterial positions were left-anterior and right-posterior as expected but they were anteroposterior in the other.

In the very young infant it may sometimes be difficult to distinguish clinically between d-transposition and pulmonary atresia. The favoured clinical diagnosis in 6 infants in this study was pulmonary atresia (Table 4) and the echocardiographic demonstration in 4 of these infants of 2 arterial roots in the typical position was most helpful in supporting the diagnosis of d-transposition and excluding pulmonary atresia.

We have not found the simultaneous recording of both semilunar valves to be specific for d-transposition (Dillon *et al.*, 1973), and we agree with others that this is a nonspecific finding (Paquet and Mullins, 1975; Hagler, 1976; Laird and Shelton, 1976). Fig. 3 illustrates this finding in a cyanosed premature infant with a persistent ductus arteriosus and normally-related great arteries. When the anterior wall of the left-anterior artery is properly recorded only the left-anterior semilunar valve is seen.

Recording of the timing of semilunar valve closure may increase the accuracy by identifying the arteries in many cases with d-transposition (Hirschfeld *et al.*, 1975), but may not be reliable in the young infant (Hagler, 1976). We have not applied this technique routinely in infant studies: in the acute situation, when rapid conclusions were required before further investigation, it often proved impossible to record semilunar cusp closure adequately. It may, however, be a particularly useful aid to the identification of great arteries when the orientation of the heart is abnormal, as for example, in dextrocardia. Fig. 4 shows the chest *x*-ray film of a mildly cyanosed 8-day-old infant with dextrocardia associated with an anterior diaphragmatic hernia through the foramen of Morgagni, and in whom a complex cardiac anomaly including d-transposition was suspected clinically. Echocardiography showed normal atrioventricular valves, septum, and ventricular cavities, and the positions of the great arterial roots were right-posterior and left-anterior. The left atrioventricular valve was continuous with the posterior wall of the posterior great artery. The QRS closure time of the semilunar cusps was 11 ms longer for the anterior than for the posterior great artery (Fig. 5). These findings strongly supported normally-related great arteries and were against a complex anomaly. The final diagnosis was situs solitus with secondary dextrocardia, ventricular d-loop, large atrial septal defect, and small muscular ventricular septal defect.

The dimension of the posterior pulmonary artery in d-transposition is usually larger than that of the anterior aortic root (Solinger *et al.*, 1973) and this was so in our study (Table 3). A small posterior root may, however, indicate the presence of d-transposition with pulmonary stenosis (Godman *et al.*, 1974), and the relative sizes of the arterial roots do not prove their identity. A small aorta might indicate the presence of aortic stenosis or coarctation of the aorta, and it is interesting to note that the smallest aortic dimension in Table 3 was associated with severe coarctation of the aorta. We have not been able to predict the presence of a ventricular septal defect or persistence ductus arteriosus from the echocardiographic findings. Admittedly we have made few measurements of left atrial size in patients with free communications but there was no trend to a larger diameter in those measured. Nor have we seen abnormal left atrioventricular valve movement, indicating left ventricular outflow obstruction (Nanda *et al.*, 1975), in young infants. One infant, however, had developed obstruction because of this mechanism (similar to that seen in idiopathic hypertrophic subaortic stenosis) by 6 months of age.

Echocardiography in the infant is a demanding discipline and its proper use requires an appreciation of its limitations as well as its advantages. Establishing the great arterial positions depends on the judgement of the direction of the transducer beam at the time of the examination and this is not infallible. Most incomplete echocardiographic assessments occurred early in the study. However, there are still occasions when it has been technically impossible to derive all information, and the unexplained failure to record satisfactorily the normal ventricular septum in one infant and a pulmonary arterial root of good size in another occurred later in the series. All negative echocardiographic observations, particularly in the presence of a complex cardiac anomaly, should therefore be regarded with reservation.

Atypical bilateral conal development may occur in 6 per cent of cases with d-transposition (Van Praagh *et al.*, 1971) and these cases would be expected to show displacement of the left atrioventricular valve from the posterior wall of the posterior arterial root. Satisfactory scans supporting a close left atrioventricular valve—posterior root relation were recorded in 84 per cent of infants in this study. However, there was true left atrioventricular valve—posterior root discontinuity in only 3 of the 7 infants in whom this scan was not achieved. It was technically impossible to scan from the left atrioventricular valve to the posterior root in the other 4 though they were closely related.

The advantages of continuous strip records over polaroid films are obvious (Godman *et al.*, 1974), but we do not consider the latter without value. It is not feasible to record the timing of semilunar cusp closure with polaroid film and records of the various dimensions and scans are less satisfactory. However, polaroid records do give rapid information about the atrioventricular valves, septum, and great arterial roots which is useful in the evaluation of d-transposition.

This study indicates that echocardiography adds significant information to the clinical assessment in over 80 per cent of infants with d-transposition without exposing them to risk or discomfort. On the other hand the technique requires expertise and time and, as the infants still require cardiac catheterisation, it may be questioned whether or not the contribution of echocardiography is sufficient to justify its use. We believe it is because a better appreciation of the intracardiac anomaly allows catheterisation to proceed more speedily and efficiently, and helps to direct angiocardiography along the most informative lines, minimising the insult to the infant. The same advantage applies to those patients in whom d-transposition is unlikely but cannot be excluded on clinical grounds. In those with hypoxia from non-cardiac causes cardiac catheterisation can usually be avoided, and in those with complex lesions echocardiographic information is helpful during the catheter study.

Real-time two-dimensional imaging has made a significant advance in the elucidation of ventriculo-arterial connections (Henry *et al.*, 1975; Maron *et al.*, 1975). However, until this becomes more readily available, the single-transducer technique should contribute significantly to the early management of at least 80 per cent of infants with d-transposition.

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Two-dimensional echocardiography in diagnosing tricuspid atresia[1]

Differentiation from other hypoplastic right heart syndromes and common atrioventricular canal

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SUMMARY Echocardiographic studies were performed in 8 patients with tricuspid atresia, 3 patients with other types of hypoplastic right heart syndromes, and 5 patients with common atrioventricular canal. Echocardiographic searching was performed mainly along the horizontal section at the level of the membranous septum of the heart. Conventional and two-dimensional (cross-sectional) echocardiograms were recorded. The findings were compared with those from the echocardiograms of 25 healthy subjects, 17 patients with mitral valve disease, and 3 patients with congestive cardiomyopathy who served as a control group as they had normal arrangements of the intracardiac structures.

In the control group, the annular ends of the anterior mitral and tricuspid valve leaflet echoes were the interatrial septum and the right anterior wall of the heart echoes, respectively.

In tricuspid atresia, a thick echo was detected in the tricuspid area. This echo did not open during diastole and was interpreted as indicating the atretic part of the tricuspid orifice. The anterior leaflet of the detectable single atrioventricular valve echo was attached to the interatrial septal echo.

In hypoplastic right heart syndromes other than tricuspid atresia, findings such as a minute right ventricle and a large left ventricle resemble those in tricuspid atresia. However, the tricuspid valve echo was detected and indicated to be open on the two-dimensional echocardiogram.

In common atrioventricular canal, the anterior leaflet of the detectable single atrioventricular valve echo was attached to the right anterior wall echo of the heart. The echo of the interventricular septum was detected in the apical area in 2 patients and not detected at all in the others.

As mentioned above, the echocardiographic features along the horizontal section were different among the control group, those with tricuspid atresia, hypoplastic right heart syndromes apart from tricuspid atresia, and common atrioventricular canal, and are thought to correspond to the anatomical differences.

Tricuspid atresia is defined as congenital complete absence of the right atrioventricular valve with hypoplasia of the right ventricle (Edwards and Burchell, 1949; Astley *et al.*, 1953; Keith *et al.*, 1967). As half of the patients die in the first 6 months of life (Keith *et al.*, 1967; Dick *et al.*, 1975), it is desirable to diagnose this malformation exactly as soon as possible in the early days of life. While the conventional non-invasive examinations such as electrocardiography and chest *x*-ray film offer diagnostic information for this malformation, there are some cases in which these conventional examinations do not produce the characteristic findings (Kroop and Grishman, 1950; Gamboa *et al.*, 1966; Dick *et al.*, 1975). Therefore, the exact diagnostic method is angiocardiography. However, as an

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invasive examination carries some risk to the newborn, a new non-invasive method for diagnosing cardiac malformations is needed.

Echocardiography has proved to be a useful aid for diagnosing congenital heart diseases (Lundström and Edler, 1971; Dillon *et al.*, 1973; Nimura *et al.*, 1974; Popp *et al.*, 1974; Solinger *et al.*, 1974; Matsumoto *et al.*, 1975; Murphy *et al.*, 1975). In tricuspid atresia, a small right ventricle, a large left ventricle, and an absent tricuspid valve echo are noticed to be the characteristic features in the echocardiogram (Chesler *et al.*, 1970; Meyer and Kaplan, 1972; Godman *et al.*, 1974). However, as an absent tricuspid valve echo does not always mean an absent tricuspid valve, it is difficult to distinguish tricuspid atresia from other hypoplastic right heart syndromes (Godman *et al.*, 1974). Moreover, unless the ventricular septal echo is identified on the echocardiogram, the findings resemble those in cases of a single ventricle with common atrioventricular canal (Chesler *et al.*, 1970). The aim of this study is to differentiate tricuspid atresia from other malformations based on anatomical points using M-mode scan and two-dimensional echocardiography.

Subjects and methods

Eight patients with tricuspid atresia, aged from 2 months to 22 years, were examined. The diagnoses were confirmed by angiocardiography, showing that 5 patients were type Ib and the other 3 patients were type Ia, Ic, and IIc, respectively (Keith *et al.*, 1967). The atrial septal defect was large in all patients. All were treated by a shunt operation except for one. The patient with type IIc had a comparatively large right ventricle for tricuspid atresia.

Patients with hypoplastic right heart syndromes apart from tricuspid atresia, and those with common atrioventricular canal, and certain other subjects were also examined for comparison. There were 3 patients with hypoplastic right heart syndromes without tricuspid atresia; 2 of them, ages 6 months and 7 years, had pulmonary atresia with normal aortic root, and the other, age 22 years, had pulmonary stenosis, tricuspid stenosis, and atrial septal defect. The diagnoses were confirmed by catheterisation and angiocardiography. There were 5 patients with common atrioventricular canal, ranging in age from 6 months to 6 years; angiography showed that 3 of them had no interventricular septum. As controls, the other subjects, without intracardiac malformations, were 25 healthy children and adults, 17 patients with mitral valve disease, and 3 patients with congestive cardiomyopathy.

A commercially available ultrasonograph, an Aloka SSD-30B, was used with a 2·25 MHz transducer, 10 mm in diameter, with a pulse repetition rate of 1500 Hz. This equipment allows one to record both conventional and two-dimensional echocardiograms by switching modes of display. The two-dimensional echocardiogram was obtained by an electrocardiograph-triggered B-Mode method (Ebina *et al.*, 1967; King, 1973). This method has been described previously by Beppu *et al.* (1976).

The patients were examined in the supine position, during relaxed respiration. As the scan was a manual compound one, the echocardiographic searching could be made from various places along the selected section plane in the chest wall, even from different interspaces or from the right sternal border (Fig. 1). The transducer was usually placed in the left intercostal space and also on the right interspace and the sternum, if necessary, for the echoes to be obtained clearly. The horizontal section at the level of the membranous septum of the heart was selected for the echocardiographic scans, as previously reported (Beppu *et al.*, 1976).

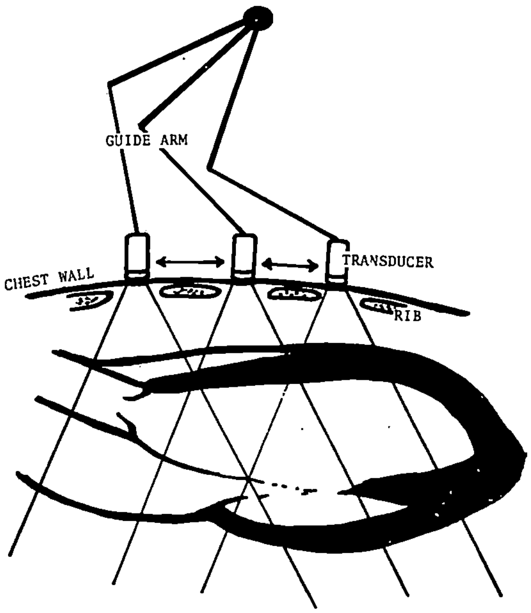


Fig. 1 *The transducer is attached to the end of the guide arm giving reference to its position and angle. As the scan is a manual compound one, the transducer can be placed in various sites on the chest wall to record echoes of a wide area of the heart.*

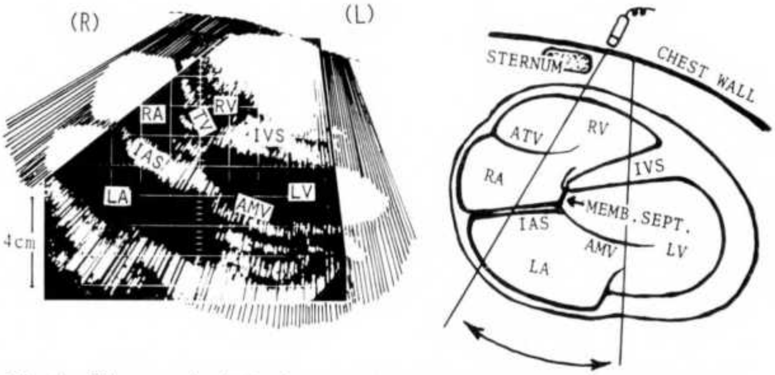


Fig. 2 *The normal relation between intracardiac structures in the horizontal section at the level of the membranous septum of a 63-year-old woman with congestive cardiomyopathy.* Left, *a two-dimensional echocardiogram, viewed from caudal, in late systole. The interventricular and interatrial septa, and the mitral and tricuspid valves are seen. The anterior mitral leaflet continues into the interatrial septum without interruption. The anterior tricuspid leaflet echo runs from the right anterior to the membranous portion.* Right, *a schematic drawing of the horizontal section of the heart. IVS, interventricular septum; IAS, interatrial septum; TV, tricuspid valve; AMV, anterior mitral valve leaflet; MEMB SEPT, membranous septum; RV, right ventricle; RA, right atrium; LV, left ventricle; LA, left atrium.* (From Beppu *et al.*, 1976, *British Heart Journal*, **38**, 911.)

Results

The two-dimensional echocardiographic features at the level of the membranous septum in cases without malformations were the same as those previously described (Beppu *et al.*, 1976).

In cases without malformations, the horizontal two-dimensional echocardiogram showed the interventricular and the interatrial septa and the mitral and the tricuspid valve echoes (Fig. 2). Each echo seemed to lead towards a central site. The site where these echoes meet is the membranous septum, but the echo of this part was not usually recorded clearly. Because the membranous septum lies almost perpendicular to the chest wall and is almost parallel to the ultrasound beam, the ultrasound is

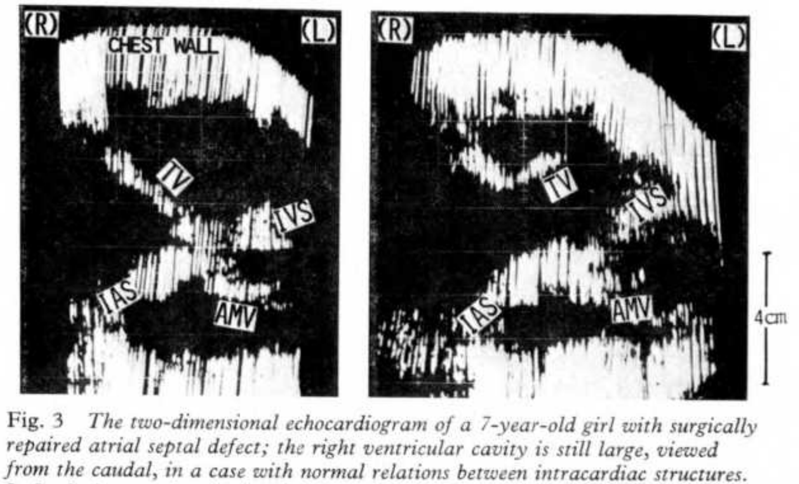


Fig. 3 *The two-dimensional echocardiogram of a 7-year-old girl with surgically repaired atrial septal defect; the right ventricular cavity is still large, viewed from the caudal, in a case with normal relations between intracardiac structures.* Left, *during systole, the tip of the anterior tricuspid valve leaflet echo attaches to the membranous portion.* Right, *during diastole, the tip of the anterior tricuspid valve leaflet echo separates from the membranous portion.*

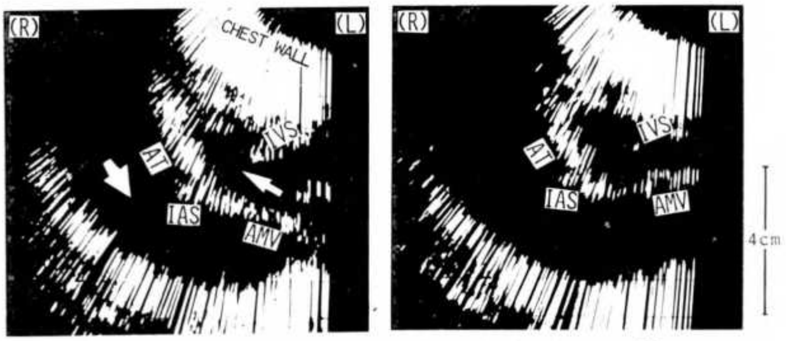


Fig. 4 *The horizontal echograms in tricuspid atresia in a 3-year-old boy.* Left, *during systole, the anterior mitral valve leaflet echo was in the closing position. The echo of the anterior mitral valve leaflet continued into the interatrial septum echo as in normal cases. The interatrial septum echo ended abruptly in the atrial area, demonstrating atrial septal defect (indicated by the white arrow on the left). From the membranous portion to the right anterior wall of the heart, a thick echo was recorded. In this patient, the echo of the interventricular septum was not recorded near the membranous septum, demonstrating ventricular septal defect (indicated by the white arrow on the right).* Right, *during diastole, the anterior mitral valve leaflet was in the opening position. However, a thick echo in the area corresponding to the tricuspid orifice did not move or separate from the membranous portion. AT, atretic part of the tricuspid orifice.*

not reflected sufficiently. The echo of the anterior mitral valve leaflet was always continued into the echo of the interatrial septum. The echo of the anterior tricuspid valve leaflet ran from the anterior wall of the heart to the medial end of the interventricular septum echo. The two-dimensional echocardiogram during diastole showed the tip of the anterior tricuspid leaflet separated (or opened) anteriorly from the membranous portion (Fig. 3).

(1) TRICUSPID ATRESIA

Echocardiography indicated a small right and a large left ventricle in all patients except the one with type IIc. Two-dimensional echocardiography along the horizontal section at the level of the membranous septum showed that the echo of the anterior mitral leaflet continued into the interatrial septum as in normal subjects (Fig. 4). A thick echo, between the annular end of the anterior mitral valve leaflet

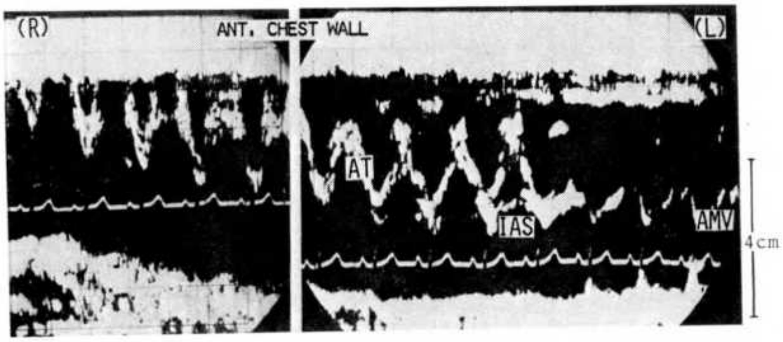


Fig. 5 *M-mode scan from right to left at the level of the membranous septum of the heart. On the right side of the heart, the anterior wall of the heart moved posteriorly during diastole. Scanning leftward, this echo separated from the anterior wall increasing its amplitude. Behind this echo, the interatrial septum echo suddenly appeared, joining up with the anterior mitral valve leaflet echo. The echo recorded from the right anterior wall of the heart to the annular end of the anterior mitral valve leaflet did not show the normal anterior movement of the tricuspid valve during diastole.*

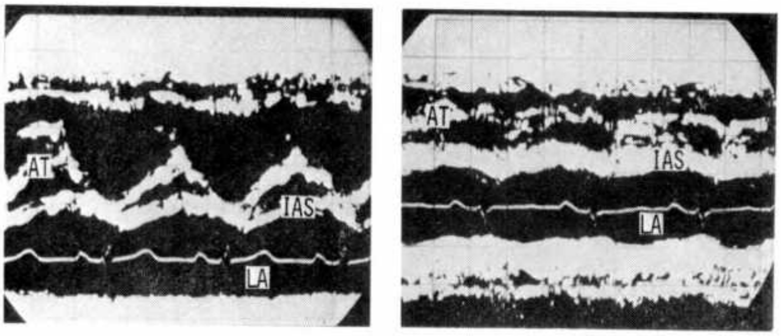


Fig. 6 *In 2 patients with tricuspid atresia, the echo of the atretic part of the tricuspid orifice showed a tiny two-peaked pattern during diastole.*

and the right anterior wall of the heart, was detected. The anatomical site of this echo corresponded to that of the anterior tricuspid leaflet in normal subjects. However, the echo did not separate from the membranous portion during diastole (Fig. 4, right). The echo of the interatrial septum ended abruptly in the atrial area, indicating atrial septal defect (Matsumoto *et al.*, 1975; Beppu *et al.*, 1976).

M-mode scan along the horizontal section showed the same findings as were seen in two-dimensional echocardiography. On the right, the anterior wall of the heart moved posteriorly during diastole. From there to the annular attachment of the anterior mitral valve leaflet, a thick echo with a wavy pattern was recorded. This echo corresponded to the tricuspid valve in a normal heart; however, it did not move like the atrioventricular valve. Behind this echo, the interatrial septum echo appeared abruptly and continued to the left to the anterior mitral valve leaflet echo (Fig. 5). The echo between the right anterior wall and the membranous portion showed no anterior movement during diastole in all except 2 patients with tricuspid atresia, and in these 2 patients, a tiny two-peaked pattern was seen during diastole (Fig. 6).

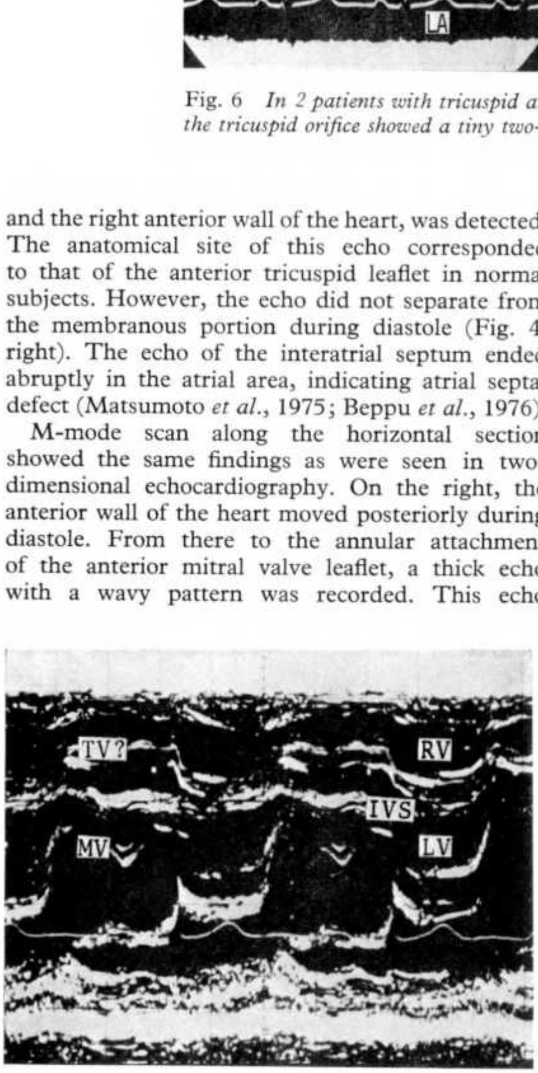


Fig. 7 *Conventional echocardiogram in a patient with tricuspid atresia type IIc. The right ventricle was comparatively large. In this cavity, an echo moving anteriorly during diastole and posteriorly during systole was detected ('TV?' in figure). This motion was identical to that of the atrioventricular valve leaflet, and, therefore, this echo apparently suggests the tricuspid valve.*

In the patient with type IIc, whose right ventricle was fairly large, standard echocardiograms showed that the sizes of both the ventricles were comparatively balanced, as seen in healthy subjects (Fig. 7). In the right ventricular cavity, an echo moving anteriorly during diastole and posteriorly during systole was detected (Fig. 7). This motion was identical to that of an atrioventricular valve leaflet. Therefore, this echocardiographic finding apparently suggested that the tricuspid valve did exist and function in this patient. However, the horizontal two-dimensional echocardiograms showed the same findings among all the patients (Fig. 8). A thick echo was detected in the area corresponding to the tricuspid annulus and did not open during diastole. The echo moving like a tricuspid leaflet, mentioned above, was recorded when the ultrasound beam was directed to the middle portion of the right ventricle. As this patient had a large ventricular septal defect, a subvalvular apparatus, like the chordae tendineae, was being moved by the blood through this defect, not through the tricuspid orifice.

The above echocardiographic features along the horizontal section were detected in all patients examined except one whose membranous portion could not be recorded because of the interference from the sternum or the lung.

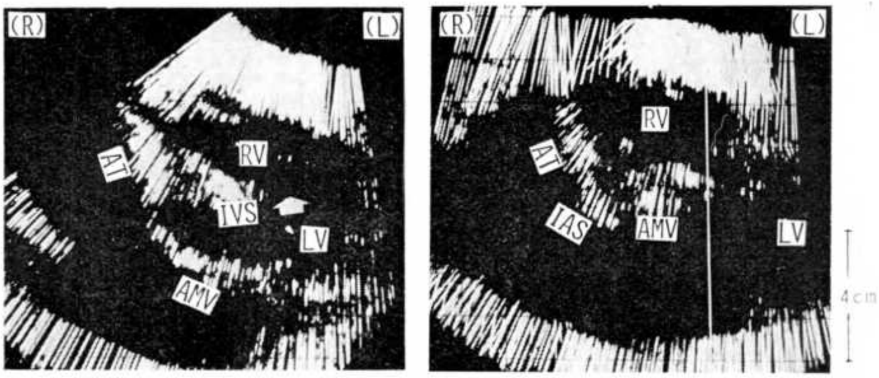


Fig. 8 *Horizontal echograms in a patient, a 22-year-old man, with tricuspid atresia type IIc (same patient as in Fig. 7).* Left, *during systole, the echo of the anterior mitral valve leaflet was closing. Between the membranous portion and the right anterior wall of the heart, a thick echo was detected.* Right, *during diastole, this echo did not move, as in other patients with tricuspid atresia. The conventional echocardiogram of Fig. 7 was recorded when the ultrasound beam was directed at the middle portion of the left ventricle, indicated by the white line.*

(2) HYPOPLASTIC RIGHT HEART SYNDROMES OTHER THAN TRICUSPID ATRESIA

In hypoplastic right heart syndromes without tricuspid atresia, a minute right ventricle and a large left ventricle were recorded by conventional echocardiography. Those features were identical to those in tricuspid atresia. Scanning toward the right of the heart, however, an echo of the anterior tricuspid valve leaflet was detected (Fig. 9, left). Its motion was so tiny that it was difficult to know whether the valve functioned and opened or not, since even in tricuspid atresia, the atretic part of the tricuspid orifice moved anteriorly slightly during diastole in 2 patients. The two-dimensional echocardiogram along the horizontal section, however, showed that the tip of the anterior tricuspid leaflet echo was separated from the medial end of the interventricular septal echo during diastole (Fig. 9,

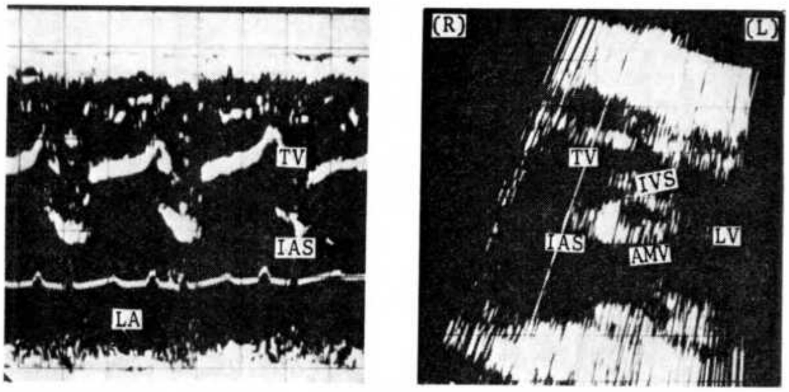


Fig. 9 *Echograms in a 6-year-old girl with atrial septal defect and persistent ductus arteriosus in addition to pulmonary atresia with normal aortic root.* Left. *an echo of the anterior tricuspid valve leaflet was recorded. It moved anteriorly slightly during diastole.* Right, *horizontal echogram at early diastole. A white line indicates the beam direction by which the conventional echogram on the left was recorded. The tip of the anterior tricuspid valve leaflet echo separated from the medial end of the interventricular septal echo, indicating that the tricuspid valve opened during diastole. The interatrial septal echo ended abruptly in the atrial area, indicating the atrial septal defect.*

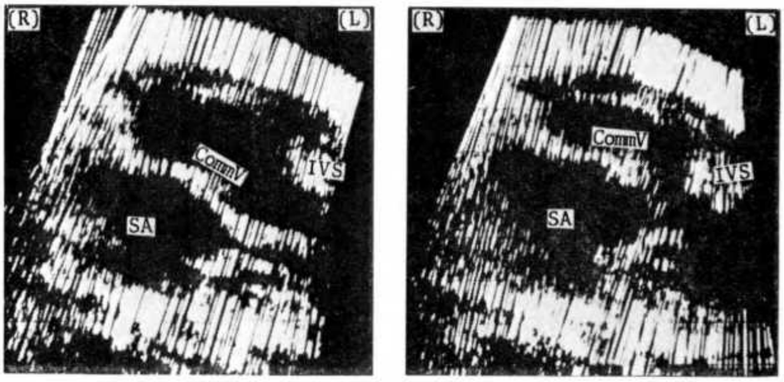


Fig. 10 *Horizontal echocardiograms in a 5-year-old girl with single atrium, persistent ductus arteriosus, and pulmonary atresia in addition to common atrioventricular canal. The echocardiograms on the left and the right are those at early systole and at mid diastole, respectively. This patient had the interventricular septum near the apical area and its echo was recorded on the echogram. The attachment site of the anterior leaflet of the only detectable atrioventricular valve was the right anterior wall of the heart. CommV, common atrioventricular valve; SA, single atrium.*

right). The anterior mitral leaflet echo was connected to the interatrial septal echo as in normal subjects. The echo of the interatrial septum ended abruptly in the atrial area, indicating atrial septal defect (Matsumoto *et al.*, 1975; Beppu *et al.*, 1976) (Fig. 9).

(3) COMMON ATRIOVENTRICULAR CANAL
In common atrioventricular canal, the conventional echocardiogram showed a large ventricle and a single atrioventricular valve echo. In the patients with an interventricular septum, the septal echo was recorded only in the apical area. On the two-dimensional echocardiograms along the horizontal section at the level of the membranous septum, however, the anterior leaflet echo of the sole atrioventricular valve was attached to the anterior wall of the heart directly (Fig. 10). These echocardiographic features were detected in 3 of the 5 patients with this malformation. In the others, the attachment site of the anterior leaflet echo was not detected because of interference from the sternum and/or lung.

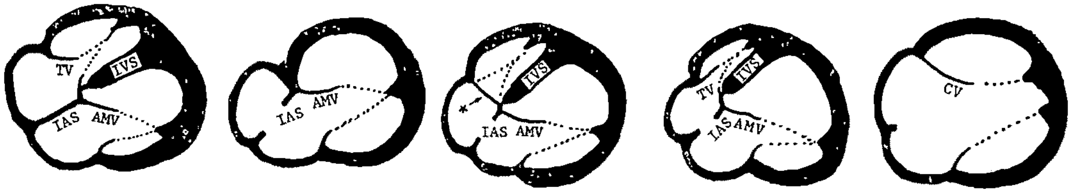
Discussion

Echocardiography, especially the two-dimensional method, is useful in diagnosing congenital heart diseases, as it shows non-invasively the anatomical relations between the intracardiac structures (Tanaka *et al.*, 1971; King, 1973; Nimura *et al.*, 1974; Sahn *et al.*, 1974; Matsumoto *et al.*, 1975; Beppu *et al.*, 1976). In tricuspid atresia, a minute right ventricle, a large left ventricle, and an absent tricuspid valve echo have been reported as characteristic features in the conventional echocardiogram (Chesler *et al.*, 1970; Godman *et al.*, 1974; Meyer and Kaplan, 1972). However, the first two findings are to be expected in hypoplastic right heart syndromes (Godman *et al.*, 1974), and the third finding does not always mean that the tricuspid valve does not exist. Moreover, if the interventricular septal echo is not recorded, it seems impossible to diagnose tricuspid atresia, because common artrioventricular canal with single ventricle offers similar findings (Chesler *et al.*, 1970).

On the other hand, in a specific case, as with the patient with type IIc who had a comparatively large right ventricle, the conventional echocardiogram showed that the right ventricle was not minute, and the echo apparently suggested that the tricuspid valve was recorded in the right ventricular cavity. Therefore, it seems to be impossible to diagnose tricuspid atresia from the criteria mentioned above.

In this study, echocardiographic differences between tricuspid atresia, hypoplastic right heart syndromes apart from tricuspid atresia, and common atrioventricular canal were investigated using two-dimensional echocardiography from the anatomical points of view (Fig. 11).

In cases with normal anatomical relations between intracardiac structures, the annular attachment of the anterior mitral and tricuspid valve leaflet echoes were the interatrial septum and the



NORMAL TRICUSPID ATRESIA IMPERFORATE TV HYPO. RIGHT HEART COMMON AV CANAL

Fig. 11 *Schematic drawings of the horizontal section of the normal heart (NORMAL), tricuspid atresia, imperforate tricuspid valve (IMPERFORATE TV), hypoplastic right heart syndromes (HYPO RIGHT HEART), and common atrioventricular canal (COMMON AV CANAL). These drawings indicate the differences of the attachment site of the functioning atrioventricular valve among these malformations. In tricuspid atresia, including imperforate tricuspid valve, the functioning atrioventricular valve is the mitral valve and its anterior leaflet connects with the interatrial septum as in normal cases. The interatrial septum is defective in every case of tricuspid atresia. In hypoplastic right heart syndromes, the right ventricle is hypoplastic; however, the tricuspid valve does exist. In common atrioventricular canal, the anterior common valve leaflet is formed by fusion of the anterior part of the anterior mitral valve leaflet and a part of the tricuspid valve. Therefore, its leaflet attaches to the anterior wall of the heart. As common atrioventricular canal is the extreme form of endocardial cushion defect, there is no connection between the interatrial septum and any leaflet of the common valve. *, imperforate membrane; CV, common atrioventricular valve.*

right anterior wall of the heart, respectively (Beppu *et al.*, 1976).

In tricuspid atresia, including imperforate tricuspid valve, anatomically, the functioning atrioventricular valve is the mitral valve. Therefore, echocardiographically, its anterior leaflet echo should connect with the interatrial septum echo, as in normal cases. In the present study, the echo of the anterior leaflet of the detectable single atrioventricular valve was attached to the interatrial septal echo as in normal cases. Thus, it was decided that this valve was not the tricuspid valve or the common atrioventricular valve, but rather the mitral valve. In the tricuspid area between the membranous portion and the right anterior wall of the heart, a thick echo was detected. Since it did not open during diastole, it was interpreted to be the structure between the right atrium and the ventricle, though this echo might include those of the atrioventricular part of the membranous septum and the ridge between the right atrium and the ventricle. Such echocardiographic findings obtained are considered to be specific to tricuspid atresia. Anderson *et al.* (1977), on the basis of their morphological study, emphasised that imperforate tricuspid valve should be distinguished from tricuspid atresia. It might be difficult clinically to distinguish imperforate tricuspid atresia from muscular atresia. However, in the patient with type IIc, the findings of the area corresponding to the tricuspid annulus were the same as those in the other patients examined. His right ventricle was fairly large and the conventional echocardiogram indicated the echo apparently suggesting the tricuspid valve in the right ventricular cavity. The echo in the right ventricular cavity should be the subvalvular tissue such as chordae tendineae. This finding indicates that this structure is an imperforate tricuspid valve (Anderson *et al.*, 1977). Thus echocardiography is considered to be advantageous in distinguishing the two types of tricuspid atresia from each other. If the feature of the atretic part of the tricuspid orifice is shown to be membranous and the annulus to be enough large for valve implantation, it might be possible for the atretic part to be excised and a new but normal circuit to be established. Two-dimensional echocardiography should offer useful information about surgical treatment.

Every case with tricuspid atresia has atrial septal defect. In the present study, the interatrial septal echo ended abruptly in the atrial area. This echo interruption is interpreted as indicating the atrial septal defect (Matsumoto *et al.*, 1975; Beppu *et al.*, 1976). If the size of the defect of the atrial septum is small in tricuspid atresia, atrial septostomy is necessary immediately after birth. Horizontal two-dimensional echocardiography may give the necessary information.

In hypoplastic right heart syndromes apart from tricuspid atresia, echocardiographic features such as a small right ventricle and a large left ventricle were similar to those in tricuspid atresia. In our patients, the echo of the anterior tricuspid valve leaflet could be detected in the area of the tricuspid orifice by conventional echocardiography, and its motion was more definite than in tricuspid atresia. However, it could not be determined whether the tricuspid valve did open or not. The two-dimensional echocardiogram during diastole showed clearly that the tip of the anterior tricuspid leaflet echo was opened, separated from the medial end of the interventricular septum echo.

In common atrioventricular canal, the conventional echocardiogram showed similar findings to those in tricuspid atresia in the point of a single atrioventricular valve echo. In order to differentiate the two, it is essential to identify the detectable single valve as either the mitral valve or the common valve. Common atrioventricular canal is an extreme form of endocardial cushion defect. In endocardial cushion defect, as the endocardial cushion is not developed, there is no continuity between the anterior mitral valve leaflet and the interatrial septal echoes (Beppu *et al.*, 1976). Moreover, anatomically, the anterior leaflet of the common atrioventricular valve is formed from the fusion of the anterior part of the anterior mitral valve leaflet and the anterior part of the tricuspid valve. Specifically, the anterior leaflet of the common atrioventricular valve attaches to the anterior wall of the heart, in the same way as the anterior tricuspid valve leaflet does in normal subjects (Fig. 11). There is no connection between the interatrial septum and any leaflet of the common valve. In this study, on the horizontal two-dimensional echocardiogram, the annular attachment site of the anterior leaflet of the common valve was shown to be the anterior wall of the heart. This configuration corresponds to the above-mentioned anatomy of this malformation.

In this study, the site of the annular attachment of the anterior leaflet echo could not be detected in one patient with tricuspid atresia and in two patients with common atrioventricular canal. In these patients, the sternum and/or lung disturbed the echocardiographic search for the site concerned. However, as the sternum is not calcified in newborns, the echocardiograms can be obtained satisfactorily through the sternum. Therefore, it should be easier to search for the attachment site of the detectable sole atrioventricular valve when the examinee is a newborn.

In summary, echocardiographic differentiation between tricuspid atresia and common atrioventricular canal is based on the difference of the attachment site of the anterior leaflet echo of the detectable single atrioventricular valve (Fig. 11). When it is the interatrial septum, the valve is the mitral valve and the malformation is tricuspid atresia. When it is the anterior wall of the heart, the valve is the common valve and the malformation is common atrioventricular canal. In hypoplastic right heart syndromes apart from tricuspid atresia, the tricuspid valve is recorded as opening during diastole. The above differentiation can be more clearly performed by two-dimensional echocardiography than by conventional echocardiography.

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British Heart Journal, 1978, **40**, 1184-1187

Severe and early stenosis of porcine heterograft mitral valve

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SUMMARY A patient who had aortic and mitral valves replaced by Carpentier porcine heterografts for bacterial endocarditis developed severe heart failure 18 days after operation. A second emergency operation revealed that the mitral prosthesis had become severely stenosed and calcified. A loud Graham Steell murmur had developed during the 12 hours before reoperation but no distinct murmurs of mitral stenosis had been detected.

Mounted porcine aortic valve heterografts are being used in increasing numbers. Occasional reports have recorded cases of failure from valvular regurgitation, usually caused by a leaflet or leaflets becoming torn, sometimes in association with infective endocarditis. We report the development of severe mitral stenosis in a stent-mounted porcine heterograft necessitating emergency replacement 19 days after initial implantation.

Case report

A 26-year-old man with no previous history of serious illness or recent dental treatment was admitted to hospital with a 3-week history of fever, malaise, arthralgia, and weight loss. On examination, he looked ill with pallor (Hb 12·1 g/100 ml), pyrexia (38·5°C), and early finger clubbing. His pulse was 120/minute, regular, of large volume and collapsing character. Systolic blood pressure was 160 mmHg with sounds changing at 45 mmHg but audible down to zero. The heart sounds were normal; grade 3/6 midsystolic and early diastolic murmurs were maximal at the left sternal edge and a grade 3/6 pansystolic murmur was maximal at the apex. Both liver and spleen were enlarged to 6 cm below the costal margin; no basal crepitations were heard and there was no peripheral oedema or elevation of jugular venous pressure. Urine microscopy revealed many red blood cells. Electrocardiography showed sinus tachycardia and distinct left ventricular hypertrophy. An *x*-ray film of the chest showed no abnormality of heart size or shape and no evidence of pulmonary congestion (CTR 135/280).

A clinical diagnosis of infective endocarditis was supported by growth of *Streptococcus viridans* in all of nine consecutive blood cultures. The valvular lesions were judged to be regurgitation of both mitral and aortic orifices, the severity of the latter being of recent origin and the result of endocarditis. Arrangements were therefore made for elective surgical replacement of the aortic valve and the patient was prepared by bed rest and initiation of treatment of the infection with benzyl penicillin 4 megaunits 6-hourly intravenously and streptomycin 500 mg 12-hourly intramuscularly. With this combination the patient's serum inhibited growth of his own organism at dilutions up to 1:1000. His general condition improved, his temperature settled, and operation was performed on the seventh day in hospital.

At operation the aortic valve was found to be tricuspid with all 3 cusps thickened and retracted. There were vegetations immediately below the noncoronary cusp and early abscess formation in the aortic root. The vegetations extended onto the aortic cusp of the mitral valve. Removal of the infection necessitated replacement of both aortic and mitral valves. Carpentier-Edwards stent-mounted porcine heterografts were used, 23 mm in the aortic position and 33 mm in the mitral position.

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Immediately after operation atrial fibrillation developed and crepitations were noted over the lung bases. Digoxin and diuretic therapy was started and parenteral penicillin and streptomycin continued. The heart sounds were normal and there was no more than a soft systolic murmur at the left sternal edge. Progress was satisfactory until the tenth postoperative day when pyrexia recurred. Eleven blood cultures were negative and though the pyrexia continued, no cause was found. On the thirteenth postoperative day the cardiac rhythm began varying between atrial fibrillation, junctional rhythm, and sinus rhythm with first degree heart block. At this time therapy was digoxin 0·25 mg daily (with blood levels within the therapeutic range), frusemide 80 mg daily with potassium supplements, parenteral antibiotic as before (with serum inhibiting the patient's organism to a dilution of 1:256), and warfarin therapy with prothrombin ratios within the range 1·8 to 2·5:1 on the majority of occasions. On the sixteenth postoperative day cough with purulent sputum was evident, with no growth on culture, but in view of continued pyrexia, parenteral cloxacillin 1 g intravenously 6-hourly and gentamicin 80 mg intravenously 8 hourly were added to treatment. Over the next 2 days there were increasing signs of left ventricular failure, decreasingly responsive to diuretic therapy. On the 18th postoperative day the patient developed cardiogenic shock, with drowsiness, tachypnoea, profuse sweating, cold extremities, oliguria, hypotension (BP 80/50 mmHg), and sinus tachycardia. The pulse was not collapsing in character but for the first time a grade 3/6 long early diastolic murmur became audible at the left sternal edge. The soft systolic murmur was unchanged but no other murmurs were heard. The severe left ventricular failure was attributed to aortic regurgitation caused by continued infection in the aortic root as evidenced by pyrexia and first degree heart block. The small pulse pressure and absence of a collapsing pulse were attributed to a low output state. Emergency surgery to replace the aortic prosthesis was decided upon and operation was performed in the early hours of the 19th day after the first operation.

At operation the pulmonary artery was noted to be tense but when the aorta was opened the aortic prosthesis appeared normal and no periprosthetic leak could be found. Even with strong suction applied to the left ventricular vent with saline in the aortic root there was no leakage of the saline through the valve. The left atrium was then opened and the mitral heterograft examined. The mitral prosthesis looked yellow in colour and when pressure was applied to the cusps it was found that there was strong resistance to opening. Though the nature of the change in the valve cusps was not apparent macroscopically, the valve was severely stenotic and was, therefore, excised. No thrombi or vegetations were present but the cusps were rigid and considerable force was required to open them. The mitral valve was replaced with a 31 mm Björk-Shiley tilting disc prosthesis. The aortic heterograft appeared satisfactory but in case the factor responsible for the mitral stenosis might later affect the aortic cusps it was decided that it too should be replaced by a Björk-Shiley prosthesis (23 mm).

The patient's progress after the second operation was uneventful. Streptomycin, cloxacillin, and gentamicin therapy were discontinued one week after operation, but a 6-week course of penicillin was completed. He was discharged home 3½ weeks after the second operation, maintained on oral anticoagulants but no other medical treatment. Six months later he was symptom free, in normal rhythm, blood pressue 130/75 mmHg and had no murmurs or cardiac enlargement (CTR 130/280). The sounds of his prosthetic valves were satisfactory and his electrocardiogram was normal.

Examination of the prosthetic aortic valve showed it to be normal apart from some fibrin thickening of the leaflets at the centre of the valve. The mitral valve leaflets, however, were extremely hard and stiff. Histology showed a layer of calcium extending from the base of each leaflet through its entire length to the edge of the valve. Calcification was thicker at the tips of each leaflet (Fig. 1a), with bands extending out towards the base (Fig. 1b).

Discussion

Several long-term reports on the follow-up of mounted porcine heterografts in the mitral position have now been published. They all report some instances of valve failure which has usually been the result of regurgitation caused by perforation of cusps, detachment of cusps from their stents, or tears in the free margin of the cusps (Carpentier *et al.*, 1974; Horowitz *et al.*, 1974; Cohn *et al.*, 1975; McIntosh *et al.*, 1975; Stinson *et al.*, 1977). Many of these instances of prosthetic valve failure have occurred in association with infective endocarditis. Several authors have also drawn attention to the presence of gradients across apparently normally functioning mitral porcine heterografts (Horowitz *et al.*, 1974; Johnson *et al.*, 1975). Overgrowth of fibrous tissue interfering with valve function has also been described (Horowitz *et al.*, 1974; Stinson *et al.*, 1974). Levitsky, in discussion following the report of Stinson *et al.* (1977) on 461 patients in whom porcine heterografts were implanted, described a 9-year-old child whose mitral porcine

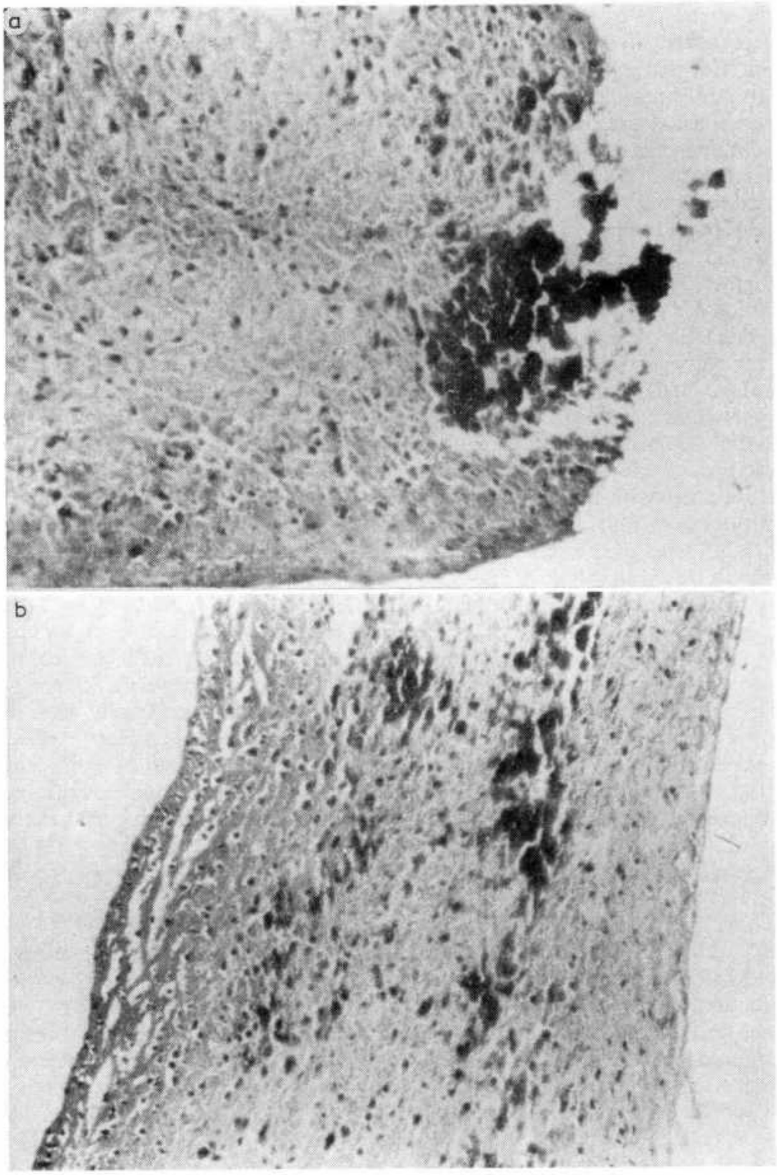

Fig. 1 *Sections from the heterograft mitral valve showing heavy calcification (dark areas) at the tip of each leaflet (a) with bands of calcification extending towards the base (b).*

heterograft was removed 19 months after operation—all the cusps were stiff with areas of calcification on both atrial and ventricular surfaces.

There are few descriptions of histological examination of glutaraldehyde stabilised porcine heterografts removed after implantation. Yarbrough *et al.* (1973) examined 7 porcine heterograft valves removed from 6 patients and 1 calf between 2 and 26 weeks after implantation. All these valves were considered to be macroscopically normal but microscopically small foci of necrosis were present in 3 of them. There was no evidence of calcium deposition in any of the valves. Horowitz *et al.* (1974) examined 4 valves recovered between 4 and 29 months after operation and found preservation of cellular architecture and structural integrity in all valves, with little histological change as compared with unimplanted specimens. Zuhdi *et al.* (1974) have confirmed the paucity of histological change in valves prepared by the stabilised glutaraldehyde process and recovered up to 6 months after insertion.

Severe and early stenosis of a heterograft in the mitral position has not been reported previously. The extent of the calcification within 19 days of insertion suggests that the heterograft valve itself may have had some defect which predisposed to its rapid deterioration.

It is clinically instructive that repeated auscultation had not suggested mitral valve dysfunction. The early diastolic murmur which first appeared 12 hours before the second operation increased to a grade 3/6 intensity and was wrongly interpreted as recurrence of aortic regurgitation and an indication for urgent further surgery. The observations at operation excluded aortic regurgitation and provided grounds for concluding that the murmur had been the result of pulmonary regurgitation caused by pulmonary hypertension secondary to the severity of the mitral stenosis as described by Graham Steell (1888).

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British Heart Journal, 1978, **40**, 1188-1189

Left anterior hemiblock masking coronary insufficiency

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SUMMARY A case is presented in which transient left anterior hemiblock masked the electrocardiographic signs of coronary insufficiency during work.

There is a well-documented observation that left anterior hemiblock is capable of concealing the electrocardiographic signs of inferior and anteroseptal infarction, but no case has been reported that shows left anterior hemiblock concealing the evidence of coronary insufficiency during exercise. The purpose of this communication is to report such a case.

Case report

A 58-year-old man was referred to our physiological laboratory for an exercise test. The patient was known to have diabetes and pain in the left shoulder on exertion suggesting the diagnosis of angina pectoris. The electrocardiogram at rest showed signs of left ventricular hypertrophy with ST segment depression of 1 mm in leads II, III, aVF, and CR 4-7 (Fig. 1). The patient performed a standardised exercise test in the upright position on a bicycle ergometer with the electrocardiographic recording from bipolar chest-head leads (CH). The exercise started at 50 Watts but was stopped after 2 minutes because of a short bout of ventricular tachycardia and an intermittent ventricular block with prominent S waves in CH 5-7. After a rest of 10 minutes the exercise was reinitiated, this time at 40 Watts with the praecordial leads as before, and with one electrode over the left clavicle, a second electrode over the right clavicle, and a third over L5 in order to record the standard leads. During work the patient experienced pain in the left shoulder and at the same time the ST segment depressed 2 mm in lead CH 3-7, and once again a transient block developed with changes in the electrocardiogram consistent with left anterior hemiblock. Each time the left anterior hemiblock appeared the ST depression was lost, with a return of this electrocardiographic evidence of coronary insufficiency as soon as the ventricular conduction returned to normal (Fig. 2). After work the praecordial leads CR 3-7 showed a downsloping ST depressed segment (Fig. 3).

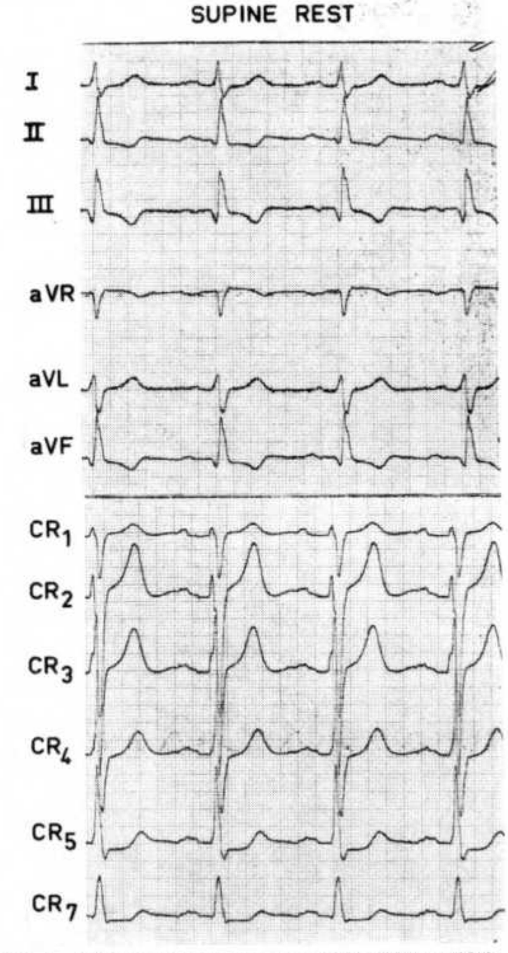

Fig. 1 *Electrocardiogram at rest with evidence of left ventricular hypertrophy and slight depression of the ST segment.*

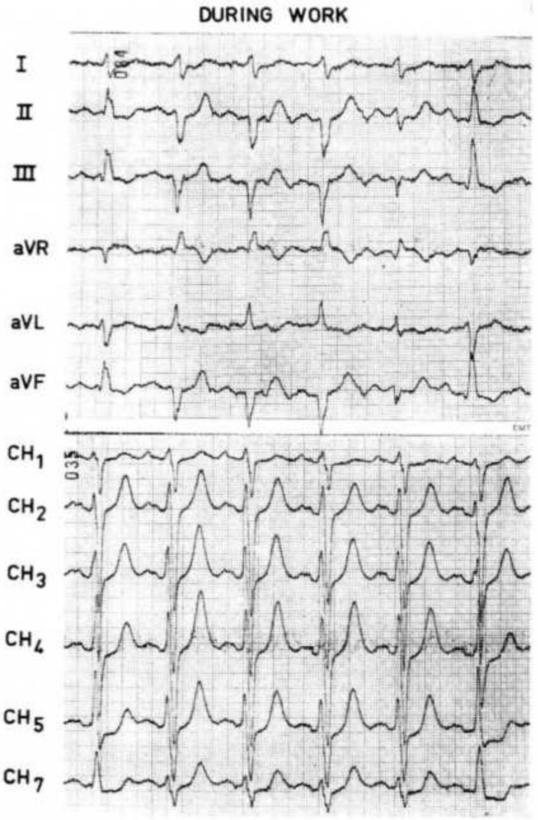

Fig. 2 *Electrocardiogram during work showing in the first and the last beat a more pronounced ST depression. The second, the third, the fourth and the fifth beat show the features of left anterior hemiblock and the return to normal of the ST segment.*

Discussion

Rosenbaum *et al.* (1972) have pointed out that left anterior hemiblock may obscure the electrocardiographic signs of inferior myocardial infarction. Recently Cristal *et al.* (1975) reported a case with anatomical and pathological findings that confirmed the hypothesis of Rosenbaum, stating that this diagnostic difficulty presupposes an intact left posterior papillary muscle. Altieri and Schaal (1973) similarly reported a case where left anterior hemiblock masked the electrocardiographic evidence of inferior and anteroseptal myocardial infarction.

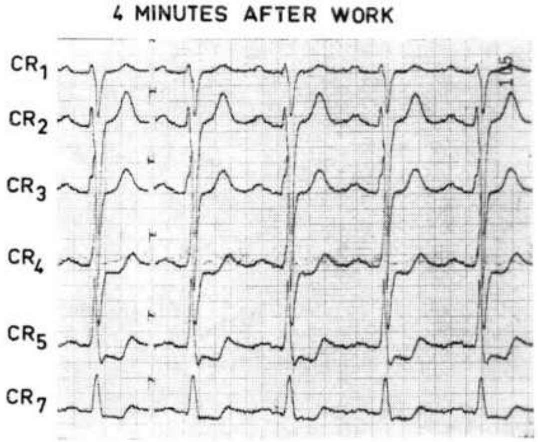

Fig. 3 *The praecordial leads after work showing downward sloping depression of the ST segment in CR 4-7 consistent with coronary insufficiency.*

The cause of the change in repolarisation in the present case is uncertain. It is possible, however, that in this patient the normal and late repolarisation of the anterior and superior wall of the left ventricle counterbalanced the vector of ischaemia originating from the lateral and inferior wall of the left ventricle. This case emphasises the need for a careful evaluation of the electrocardiographic reaction to exercise in patients with left anterior hemiblock and suspected angina, since the diagnosis of coronary insufficiency can be impossible to show unless the hemiblock is transient.

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Supravalvular aortic stenosis in a twin

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SUMMARY A case of subvalvular aortic stenosis in one of a set of dissimilar twins is reported. The case is discussed in terms of the aetiological factors involved and supports the view that supravalvular aortic stenosis is not environmental and may be genetic in origin.

The triad of supravalvular aortic stenosis, 'characteristic facies', and mental retardation was described by Williams *et al.* in 1961. Subsequently Beuren *et al.* (1964) showed that the syndrome also included peripheral pulmonary artery stenosis, systemic artery stenosis, and dental abnormalities. It was suspected by others and documented by Garcia *et al.* (1964) that as neonates these children have hypercalcaemia. In 1965 Logan *et al.* described patients who had a familial form of supravalvular aortic stenosis with normal facies and normal mental development.

This report concerns a set of dissimilar twins, one of whom had the supravalvular aortic stenosis syndrome.

Case report

The children were delivered by caesarean section at 38 weeks' gestation. The pregnancy was normal. There was no history of maternal rubella and no family history of heart disease. The boy had been referred at the age of 6 years because of tiredness and the presence of a heart murmur. The child had not fed well as a neonate and milestones were slower than the normal twin.

On examination the boy had a pleasant disposition. He had the typical facies and associated dental abnormalities of supravalvular aortic stenosis syndrome. The left brachial artery pulsation was reduced in volume in comparison with the right. The femoral artery pulsation was not delayed. The jugular venous pressure was normal. There was a palpable left ventricle impulse and a loud ejection murmur associated with a thrill at the base radiating to the neck. The remainder of the physical examination was normal, in particular there were no renal bruits or peripheral artery bruits. Developmental level, using the Gesell developmental schedule, was 4 to 5 years.

The plain chest x-ray film showed normal lung fields and normal sized heart. Skull and abdominal x-rays and intravenous urogram were normal. Bone age was normal. Electrocardiogram was consistent with moderate left ventricular hypertrophy. Full blood count, serum electrolytes, serum calcium, blood urea, and serum creatinine were normal.

The following pressures were recorded at right and left heart catheterisation (Table).

Table

Site	*Pressure mmHg*
Pulmonary capillary venous pressure	mean 9
Right pulmonary artery	20/15
Main pulmonary artery	33/15
Right ventricle	33/5
Right atrium	mean 5
Left ventricle	210/10
Proximal ascending aorta	210/95
Distal ascending aorta	155/80

Cineangiograms were performed with injections in both left and right ventricles. These showed severe supravalvular aortic stenosis extending into the arch of the aorta. There was mild stenosis at the origin of the right pulmonary artery (Figs. 1 and 2).

Physical examination, chest x-ray film, and electrocardiogram were normal in the female twin.

Discussion

Studies of diseases occurring in twins have been used to differentiate genetic and environmental factors involved in the aetiology of such disease states. Initially there was considerable speculation as to the role of vitamin D in causing the supravalvular aortic stenosis syndrome. Coleman (1965) showed that large doses of vitamin D compounds

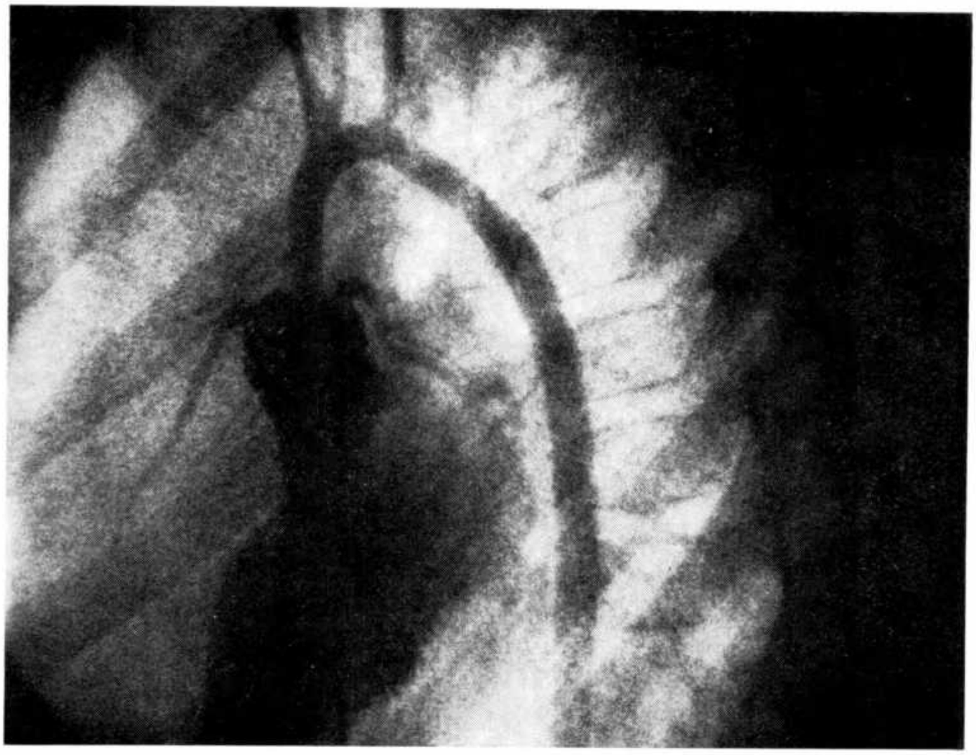

Fig. 1 *An injection has been performed in the left ventricle in the lateral projection. The severe supravalvular stenosis is shown extending into the arch and descending aorta.*

fed to pregnant rabbits consistently caused vascular lesions in their offspring. In 1966 Friedman and Roberts showed that vitamin D crossed the human placenta and they also reported vascular lesions occurring in offspring of rabbits exposed to high doses of vitamin D. In general most would agree that vitamin D excess cannot be incriminated as a cause of supravalvular aortic stenosis in humans. Fraser *et al.* (1966) are critical of the vitamin D theory, and point out the spectrum of infantile hypercalcaemia. Some children present as neonates with hypercalcaemia, the cardiac lesions being absent or unrecognised. Others present later because of the cardiovascular abnormalities; as neonates they have a history of low birthweight, poor feeding, and failure to thrive. Black and Bonham Carter (1963) have reported 5 patients who had typical facies and murmurs of supravalvular aortic stenosis and history at birth suggestive of infantile hypercalcaemia.

Absence of history of maternal rubella and only one of the twins being affected make such viral aetiology for the supravalvular aortic stenosis highly improbable.

Chromosomal abnormalities have not been detected in patients with supravalvular aortic stenosis (Beuren *et al.*, 1964).

Twin boys having typical facies with supravalvular aortic stenosis have been described (Page *et al.*, 1969). Twin girls with infantile hypercalcaemia, peripheral pulmonary artery stenosis, and hypoplasia of the aorta have been described (Wiltse *et al.*, 1966).

Underhill *et al.* (1971) from their studies of the familial form of supravalvular aortic stenosis suggested that the mode of inheritance appeared to be an autosomal dominant with incomplete penetrance in males.

Martin and Moseley (1973) reported their experience of supravalvular aortic stenosis and reviewed other published cases. In over half the cases of the 'familial' form no family history was present, so it seems that some of these cases were sporadic. There was also a large spectrum of combinations in the 'idiopathic hypercalcaemic' group. They suggested that both types might be the expression of a common metabolic defect genetically determined.

This report supports the hypothesis that the

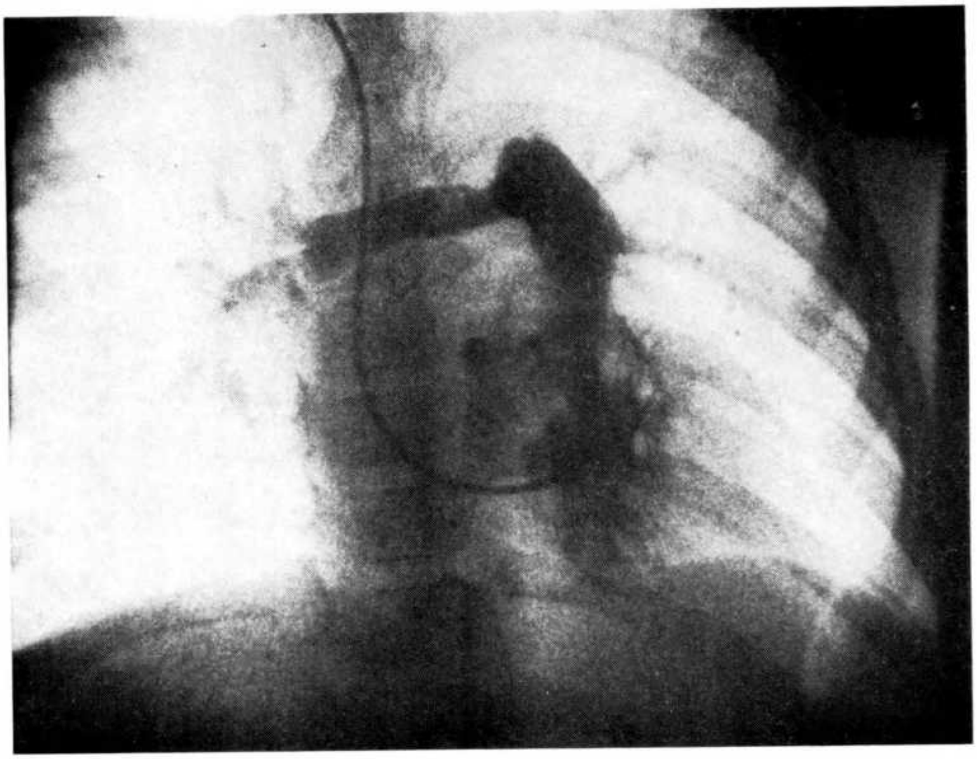

Fig. 2 *An injection has been performed in the right ventricle in a shallow right anterior oblique projection. Stenosis at the origin of the right pulmonary artery is shown confirming the haemodynamic findings. There were no other lesions in the pulmonary arteries.*

aetiology of supravalvular aortic stenosis is not environmental but is probably genetic in origin.

The length of involvement of the aorta in this patient is unusual.

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Requests for reprints to Dr Graeme Neilson, Cardiac Investigation Unit, The Prince Charles Hospital, Rode Road, Chermside, Brisbane 4032, Queensland, Australia.

Obituary

British Heart Journal, 1978, **40**, 1193

Keith Jefferson

Tragically Keith Jefferson died in October 1977 at the age of 54, at the height of his career. Renowned in his field of diagnostic cardiac radiology, he will be sadly missed at St George's and the National Heart and Chest Hospitals where he worked all his life, and also abroad since his lectures and his book made him very well known.

Educated at Oundle and Clare College, Cambridge, he went to Guy's Hospital as a clinical student and qualified in 1946; he obtained the MRCP in 1950. He chose to specialise in radiology, and after training at St George's Hospital was appointed to the consultant staff there and at the Brompton Hospital in 1956. His main interest was always the heart, so that when the new south block at the National Heart Hospital opened in 1961, Jefferson was the natural choice as radiologist. The excellence of his work was soon recognised internationally. A great part of his success was due to his ability to integrate cardiac medicine and radiology. Postgraduates flocked to his teaching sessions and as a lecturer he was outstanding. International demand for his lectures grew and he undertook many lecture tours abroad, particularly in South America. Winner of the Barclay prize of the British Institute of Radiology in 1960, he was a member of the British Cardiac Society and the Thoracic Society and in 1971 he delivered the National Heart Hospital St Cyres Lecture. He wrote extensively and won esteem in particular as co-author of *Clinical Cardiac Radiology*, the fruit of patient hours of teaching and research spread over a number of years. He will be remembered as a successful chairman of the National Heart Hospital Medical Committee, being patient and tolerant, polite but firm, and always managing to retain the friendship and respect of his colleagues.

He arrived on the London scene at a time when cardiac radiology was largely in the hands of the cardiologists who derived much information by supplementing their clinical findings with fluoroscopy. There were imperfections in their analysis of the lung fields and the new technique of angiocardiography was raising many difficulties in interpretation. Well equipped with clinical information, stimulated to analyse the lung fields by Dr George Simon, and above all working closely with the clinicians and pathologists, Keith Jefferson's opinion was widely sought by physicians and surgeons alike. This was partly due to his having worked in the cardiac department of St George's Hospital early in his career, which enabled him more easily to dovetail the history and clinical and haemodynamic findings with the radiological appearances. His approach to a problem was always simple and straightforward and indeed his most successful lecture was on the interpretation of the straight *x*-ray film. Nevertheless he was always at the front with new techniques and carried out coronary arteriography both experimentally and in the human subject at St George's before it was used elsewhere in this country.

Always a very humble and fair man with an unusually critical insight into his own work, advances in other diagnostic techniques such as nuclear medicine and echocardiography in latter years made him doubt the continuing value of radiology. It was sad that these very qualities should have led him to lose confidence in his speciality, perhaps not realising that radiology was still the gold standard and no doubt will remain so for many years.

AUBREY LEATHAM

Correspondence

British Heart Journal, 1978, **40**, 1194-1196

Early work load tests for evaluation of long-term prognosis of acute myocardial infarction

Sir,

We were interested by the work of Granath *et al.* (*British Heart Journal*, 1977, **39**, 758-763), and as we have completed a similar study but with different results the comparison of both studies could be of interest.

We studied the prognostic significance of exercise-induced ventricular arrhythmias in 302 male patients, aged 51·9 years (1 SD ± 7·3) and tested 67 days (± 16) after an acute myocardial infarction. Their 'maximal' heart rate was 143 bpm (± 24), the 'maximal' systolic blood pressure 174 mmHg (± 29), and the 'maximal' oxygen consumption 1463 ml/min (± 488). The mean follow-up period was 1114 days (± 547); total mortality was 28/302 or 9·2 per cent.

Exercise-induced arrhythmias were noted by Granath *et al.* in 17 and 23 per cent respectively, 3 and 9 weeks after infarction, whereas we found a much higher prevalence of ventricular premature beats in 50 per cent, multiform ventricular premature beats in 20 per cent, repetitive ventricular premature beats in 14 per cent, and ventricular tachycardia in 2·6 per cent (Table); the prevalence rates observed in our study are comparable with 39 per cent reported in coronary patients by Kosowsky *et al.* (1971), 50 per cent by Vuori *et al.* (1977) in post-infarction patients, and 41·7 per cent by Jelinek and Lown (1974) in 150 coronary patients who were not restricted by angina.

Table *Prognostic significance of exercise-induced arrhythmias in 302 patients who underwent an exercise test within 3 months after an acute myocardial infarction*

Arrhythmias	*No.*	*Total mortality (%)*		*P*
		With arrhythmias	*Without arrhythmias*	
Any VPB	152	10·5	8·0	NS
VPB $\geqslant$ 3/min	92	10·9	8·6	NS
Multiform VPB	59	8·5	9·5	NS
Repetitive VPB	44	4·6	10·1	$< 0{\cdot}05$
Ventricular tachycardia	8	0	9·5	NS

VPB, ventricular premature beat.

The 'low' prevalence rates reported by Granath *et al.* could be related to the low exercise performance of the subjects; their 'maximal' heart rates were only 117 and 126 at respectively 3 and 9 weeks compared with 143 in our patients.

The presence of either of these ventricular arrhythmias in our study was not associated with an increased subsequent mortality (Table). On the contrary, in patients with repetitive ventricular premature beats, mortality was even lower. Similar observations were made as to the incidence of new fatal or non-fatal cardiovascular events.

Our findings are comparable with those described by Kentala *et al.* (1975) and by Vuori *et al.* (1977); they suggest that exercise-induced ventricular arrhythmias in patients after an acute myocardial infarction could bear a different prognosis and could, therefore, have a different aetiology compared with ventricular arrhythmias detected at rest and during daily activities, clearly associated with an impaired prognosis.

The contrasting results with studies presented by Granath *et al.* (1977) could reflect a different significance of ventricular arrhythmias induced by low levels of exercise and present in only a smaller group of patients compared with the more prevalent ventricular arrhythmias described by various authors in less restricted patients.

G. De Backer, J. P. Van Durme,
Department of Cardiology,
Akademisch Ziekenhuis,
Ghent, Belgium.

References

Jelinek, M. V., and Lown, B. (1974). Exercise stress testing for exposure of cardiac arrhythmias. *Progress in Cardiovascular Diseases*, **16**, 497-522.

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Kosowsky, B. D., Lown, B., Whiting, R., and Guiney, T. (1971). The occurrence of ventricular arrhythmias with exercise as compared to monitoring. *Circulation*, **44**, 826-832.

Vuori, I., Hämäkäinen, H., and Kallio, V. (1977). Ventricular arrhythmias in exercise tests during the first year after acute myocardial infarction (abstract). *Cardiology*, **62**, 87.

This letter was shown to Dr Granath who replies as follows:

Sir,

As to the lower prevalence of ventricular arrhythmias in our material we lack information of possible differences in type of exercise or definition of ventricular arrhythmias. On the assumption that such differences can be excluded, the lower relative load in our study seems to be a reasonable explanation. The differences in prognostic importance of ventricular arrhythmias during exercise is perhaps not surprising since ventricular arrhythmias at low loads could very well be expected to be more dangerous than those appearing at higher loads only. Such an interpretation obviously makes it difficult to determine optimal test loads in these patients. The differences in choice of load between the two studies were probably influenced by differences in principles of selection as indicated by a considerably higher mean age and mortality rate in our study during corresponding follow-up periods.

Arne Granath,
Department of Clinical Physiology,
Danderyd's Hospital,
182 03 Danderyd,
Sweden.

Modified axial lead system in children

Sir,

I commend Dr MacFarlane and his colleagues for their efforts to modify McFee and Parungao's axial lead system so as to simplify electrode placement in children (MacFarlane *et al.*, 1977, *British Heart Journal*, **39**, 1102).

However, I should like to sound a note of caution. Using internipple distance rather than height might introduce a systematic error in evaluating children with widely spaced nipples (shield chest). This may be of practical significance, since Turner's syndrome, Noonan's syndrome, and the fetal hydantoin syndrome are each associated with congenital heart disease and widely spaced nipples (Smith, 1976).

W. R. Pearl,
William Beaumont Army Medical Center,
El Paso, Texas, USA.

Reference

Smith, D. W. (1976). *Recognizable Patterns of Human Malformation*, pp. 46, 50, and 346. W. B. Saunders, Philadelphia.

This letter was shown to Drs Macfarlane and Coleman who reply as follows:

Sir,

Dr Pearl is correct in sounding a note of caution on the use of internipple distance rather than height when placing the axial lead system electrodes in children with widely spaced nipples (shield chest). The simplest solution to this problem is to use the original method of McFee and Parungao (1961), namely spacing the chest electrodes in proportion to the child's height. We feel however that in children with any type of chest deformity, chest electrode placements with any lead system will be subject to error.

Peter W. Macfarlane,
Eric N. Coleman,
Royal Infirmary, and
Royal Hospital for Sick
Children, Glasgow.

Reference

McFee, R., and Parungao, A. (1961). An orthogonal lead system for clinical electrocardiography. *American Heart Journal*, **62**, 93-100.

Notices

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This course will be held on 10 to 12 November 1978 in Las Vegas, Nevada. Sponsored by the American Society of Echocardiography, American Institute of Ultrasound in Medicine and H.E.L.P. Inquiries should be sent to: Pediatric Echocardiography Course, 4340 Placita Panuco, Tucson, Az. 85718, USA 602/882-6508.

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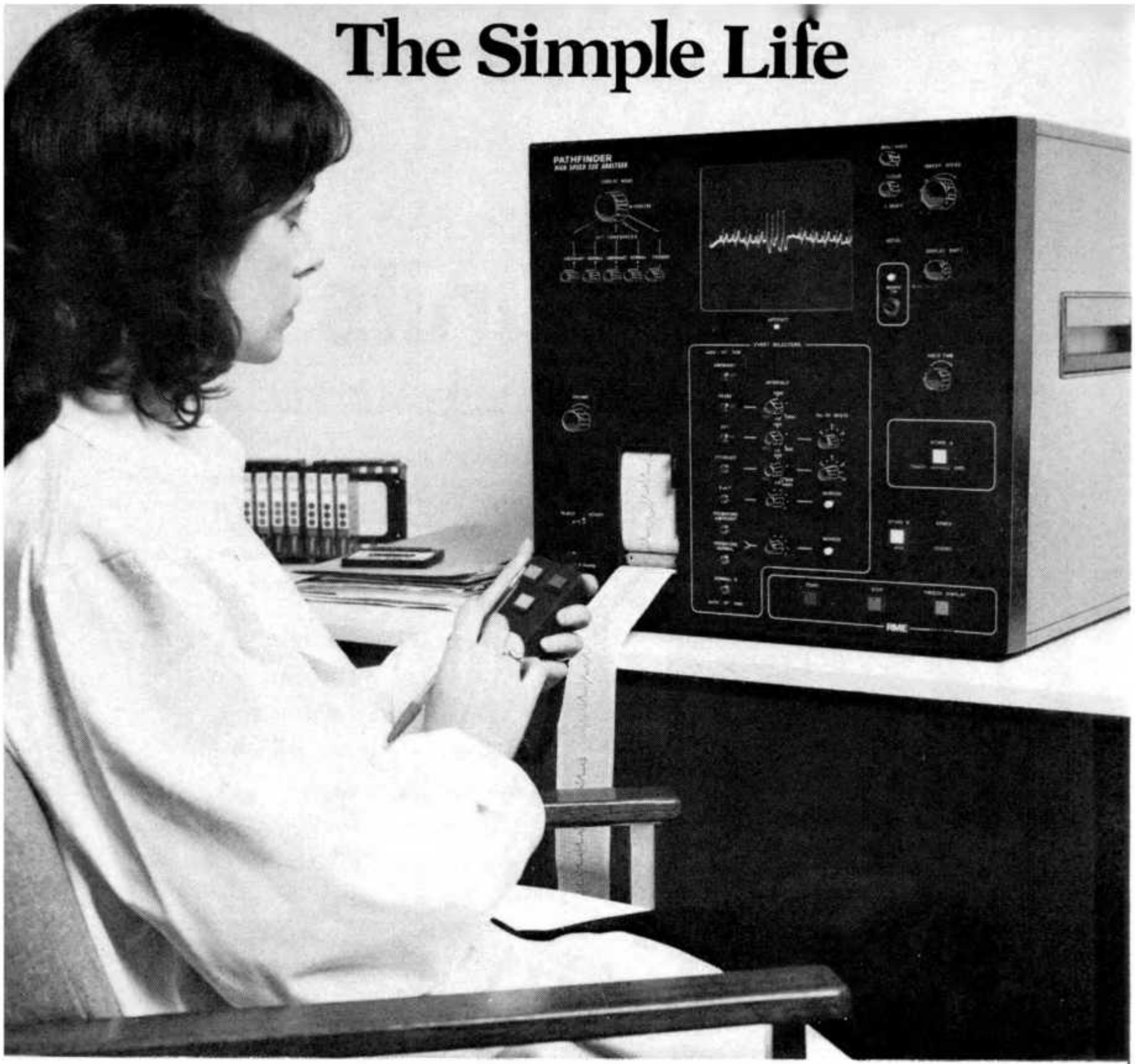

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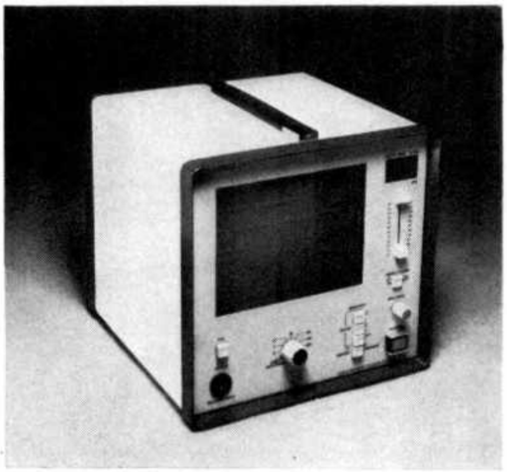

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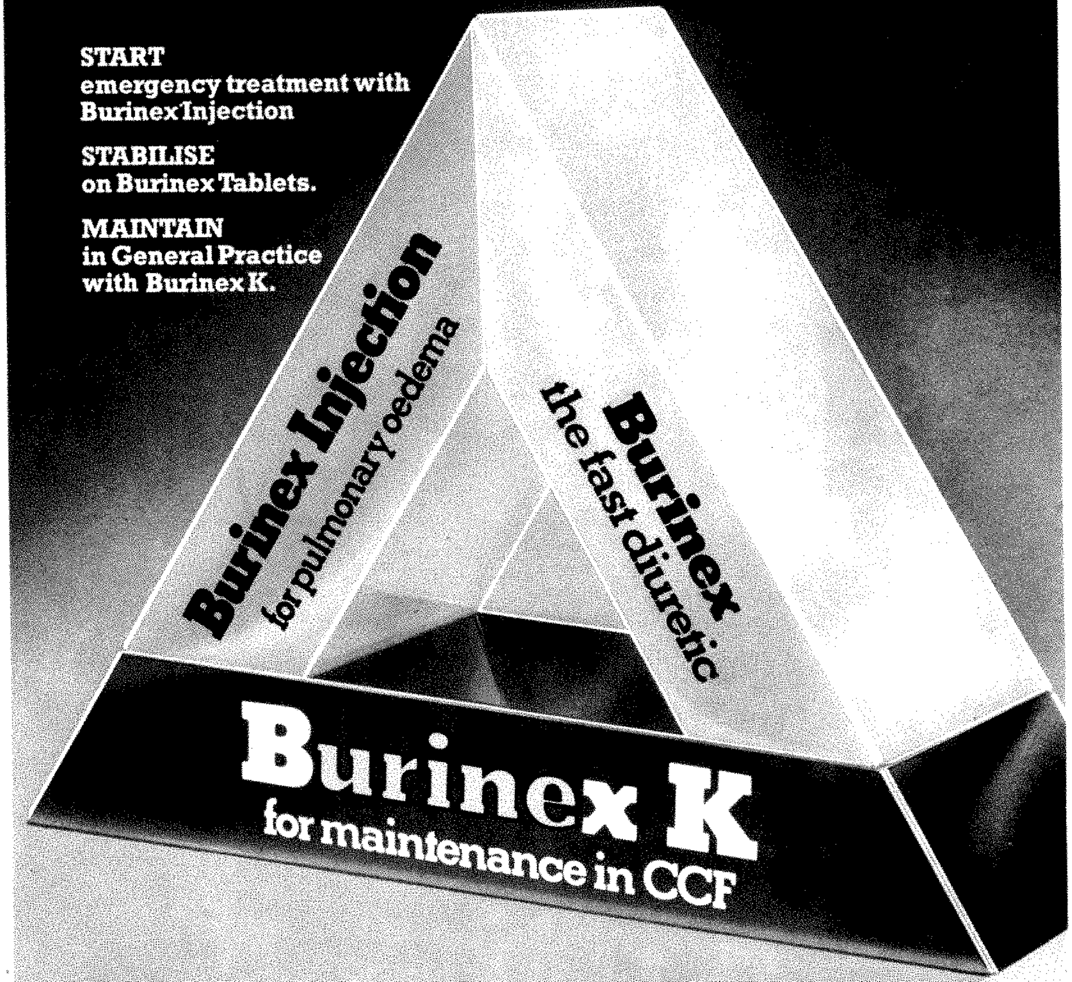

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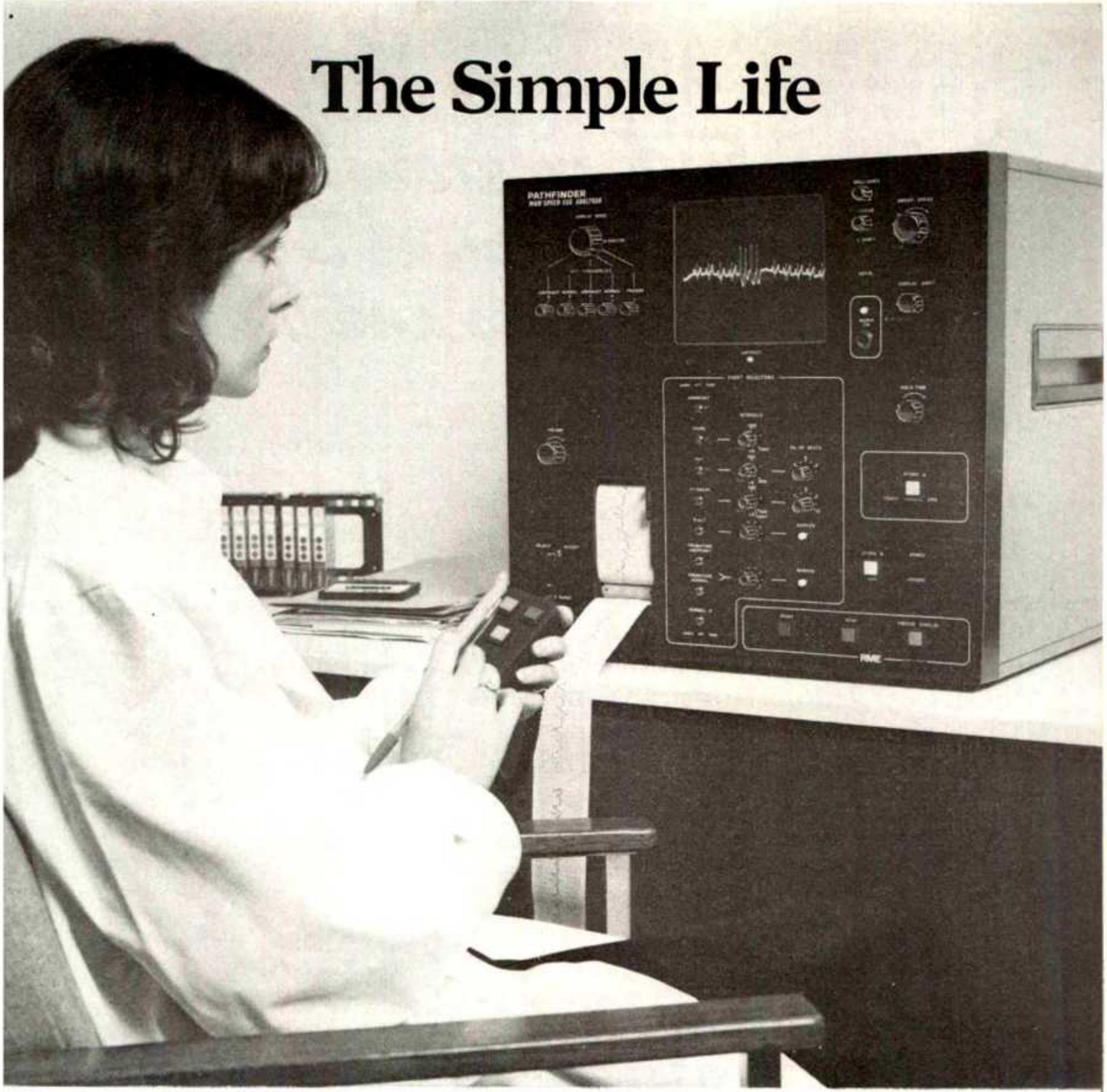

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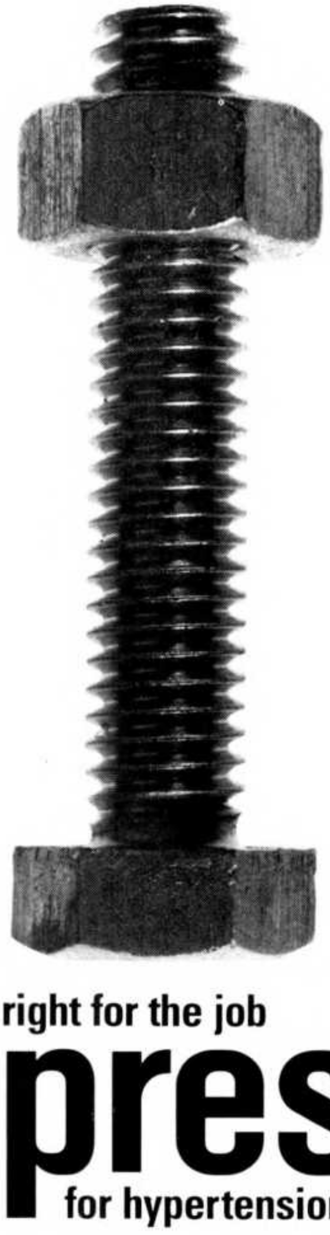

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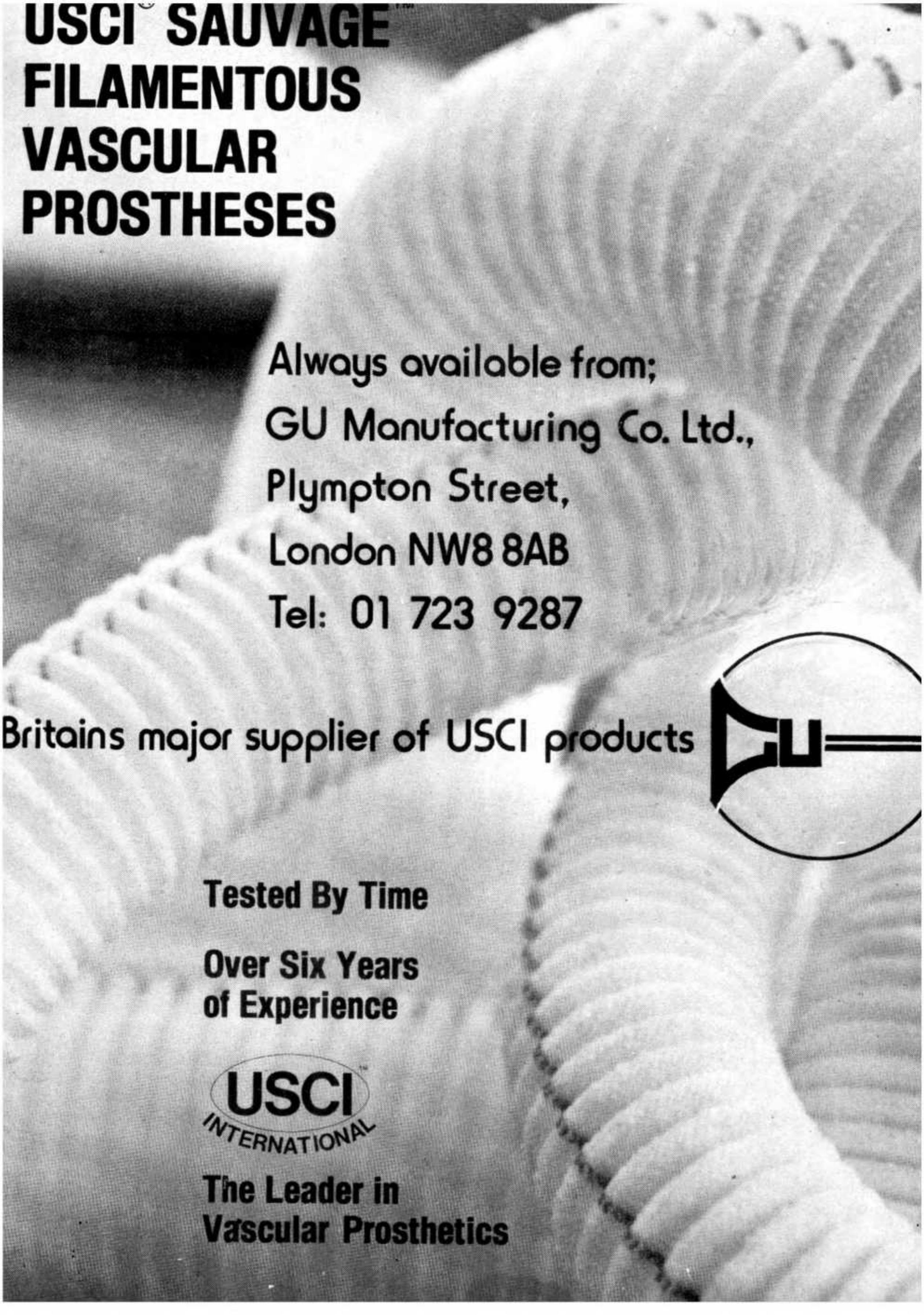

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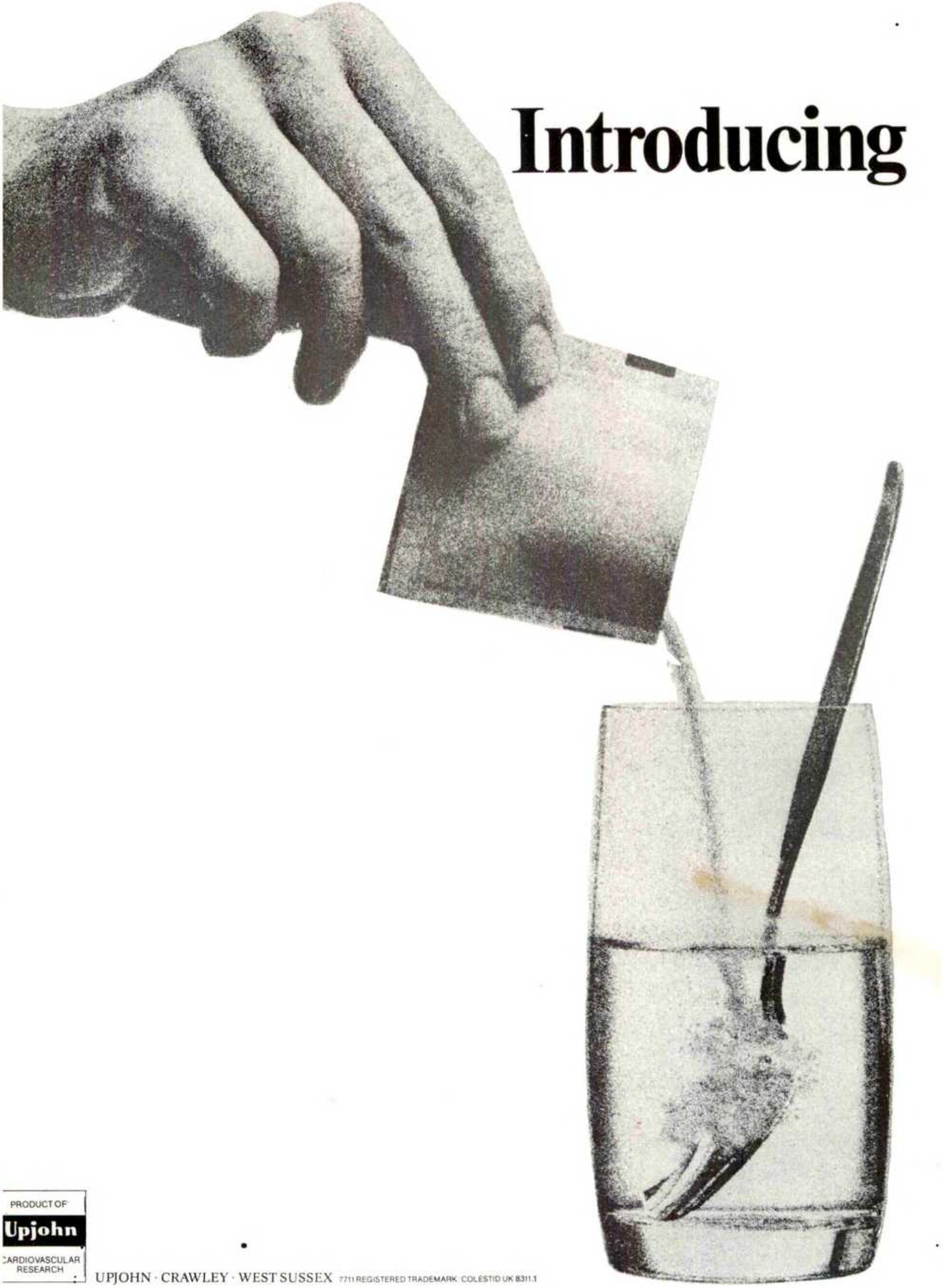

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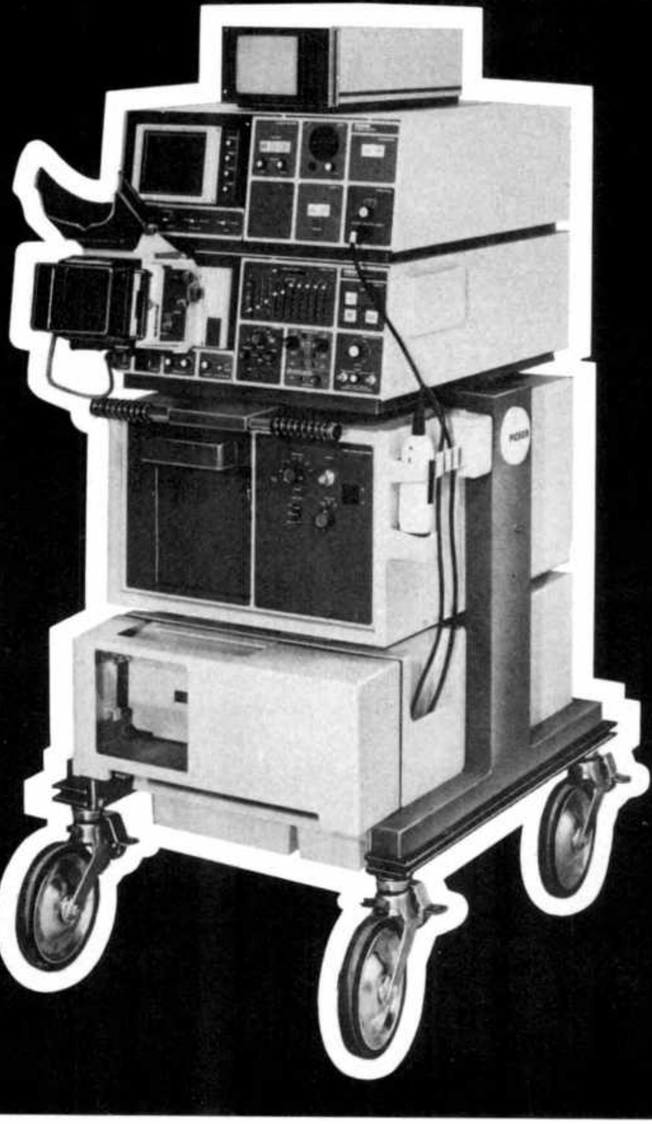

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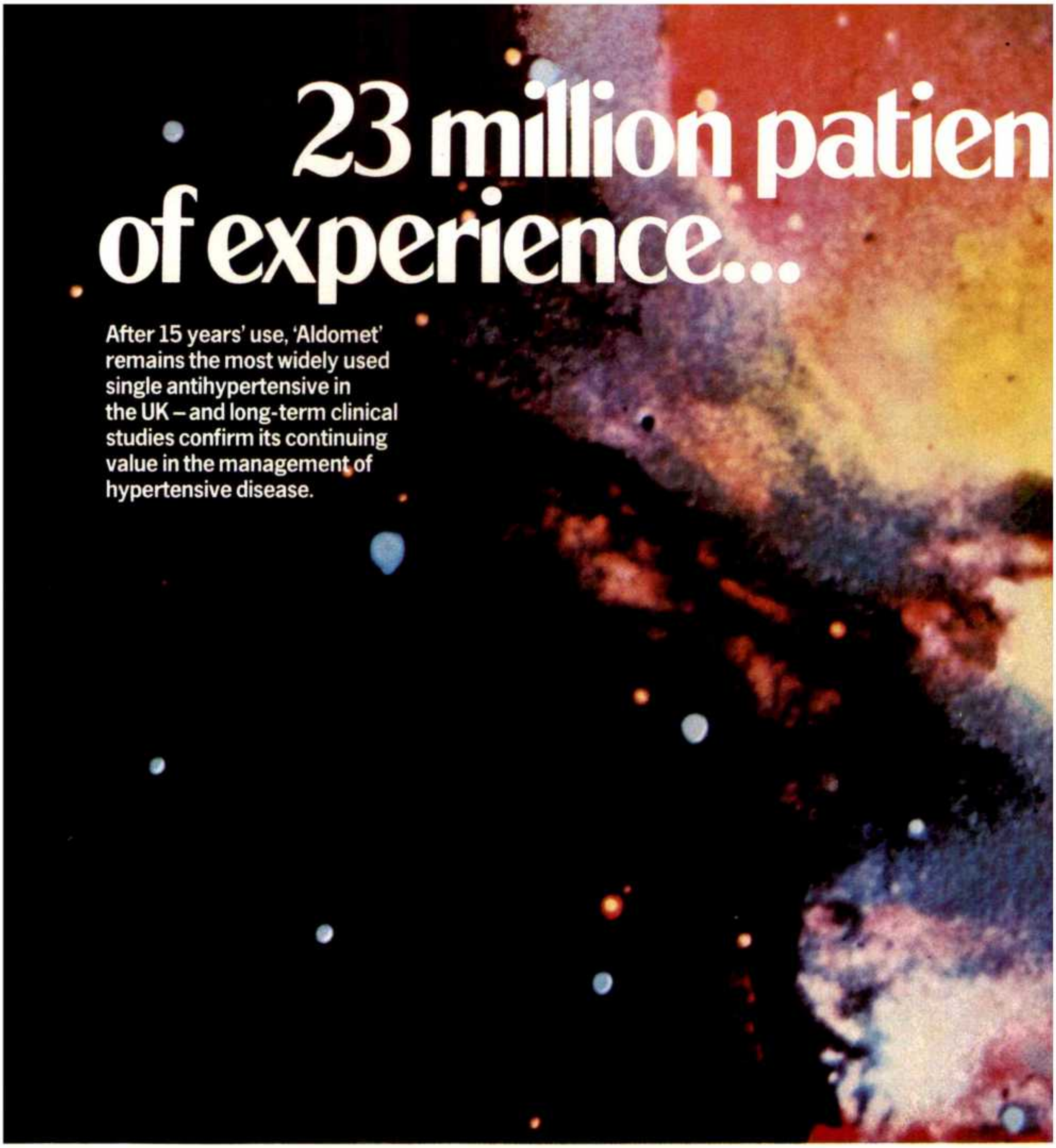

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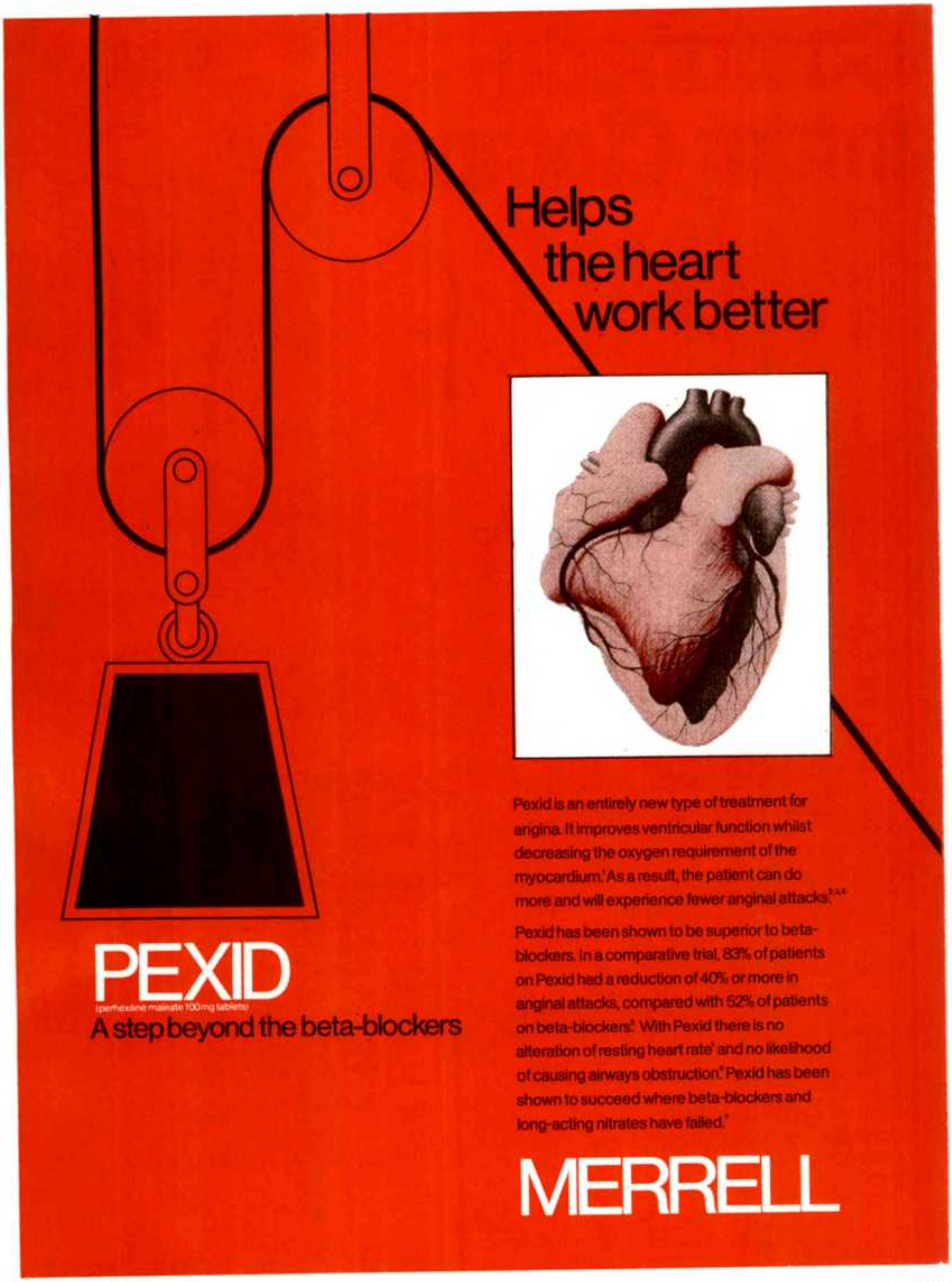
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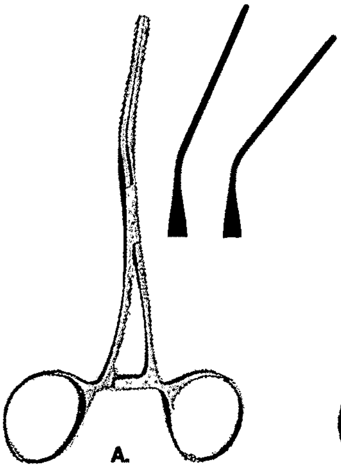
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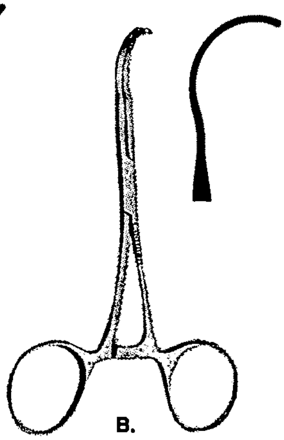
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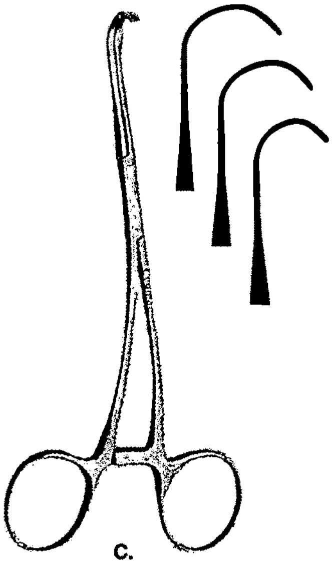
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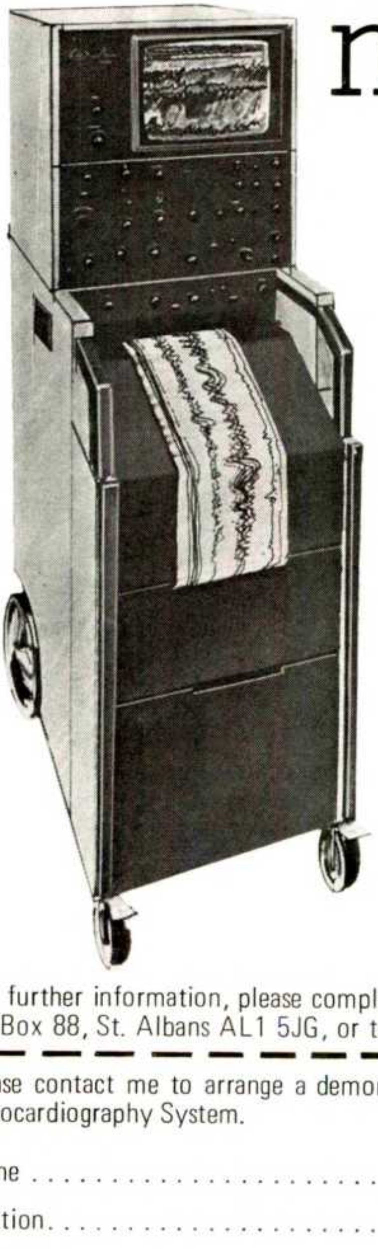

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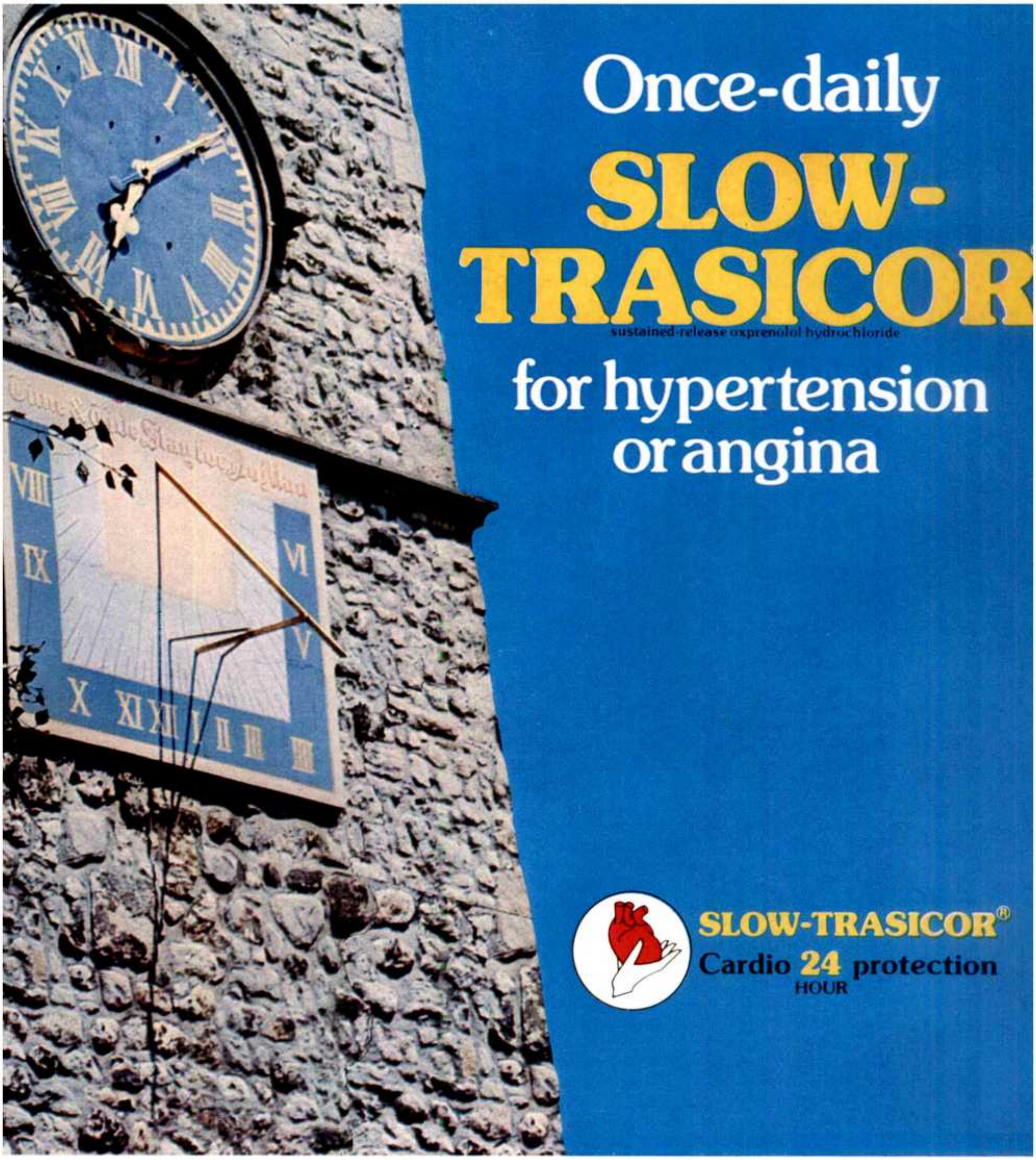
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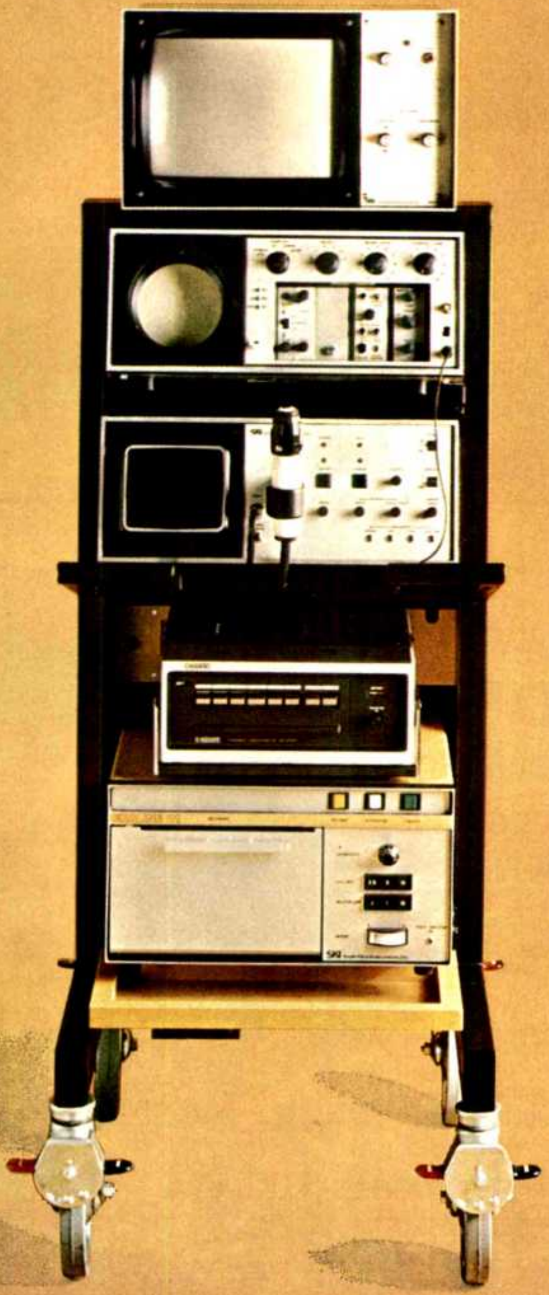

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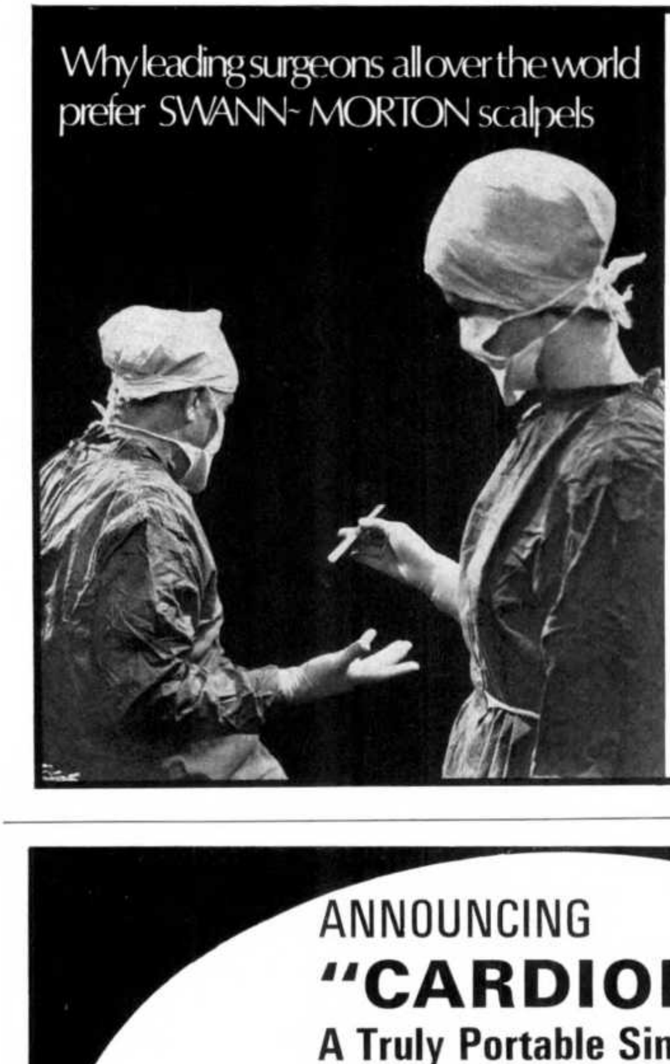
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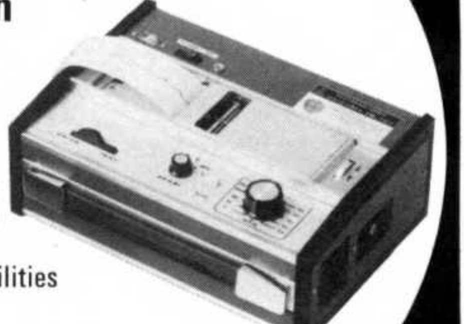

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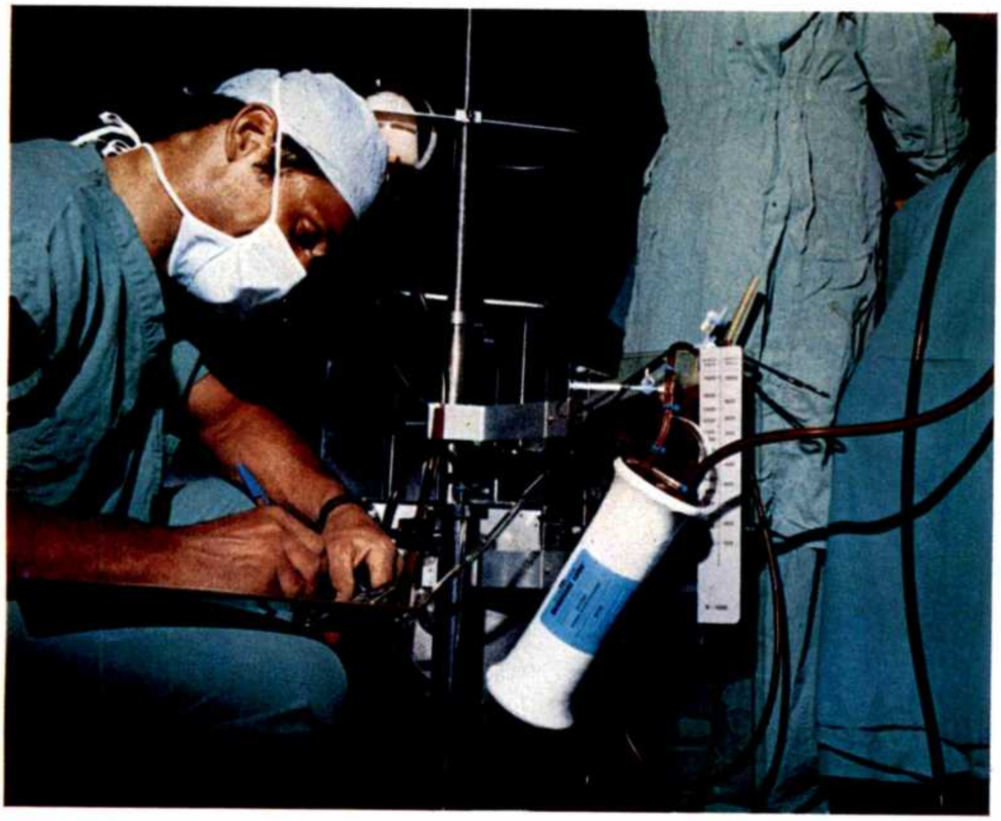

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British Heart Journal, 1978, **40**, 1197-1199

Electrical energy requirements for ventricular defibrillation

A. A. J. ADGEY

From the Department of Cardiology, Royal Victoria Hospital, Belfast

Deaths from coronary attacks constitute one of the major problems in medicine in the western world. The majority of such deaths are sudden and occur outside hospital (Bainton and Peterson, 1963; Gordon and Kannel, 1971). More than 90 per cent of sudden coronary deaths result from ventricular fibrillation (Adgey *et al.*, 1969). The prevention of ventricular fibrillation is associated with many problems. No ideal long-term oral antiarrhythmic agent is available for the patient with known coronary artery disease. Furthermore, ventricular fibrillation may be the first manifestation of ischaemic heart disease. However, in 1966, it was shown for the first time that the correction of ventricular fibrillation outside hospital is possible (Pantridge and Geddes, 1966, 1967). This led to an explosive proliferation of mobile coronary care units, particularly in the USA. Paramedical personnel operating these units concentrate on resuscitation of patients with cardiac arrest. It has become clear that involvement of the public in the technique of cardiopulmonary resuscitation is a necessary part of any pre-hospital coronary care scheme (Thompson *et al.*, 1977). Unfortunately, the limitations of cardiopulmonary resuscitation have not been sufficiently recognised. External cardiac massage and ventilation will maintain the viability of the cerebrum for 20 minutes or longer (Kouwenhoven *et al.*, 1960). However, Kouwenhoven *et al.* (1960) showed that the arterial pressure during chest compression is of the order of 80 mmHg and between compressions 10 to 20 mmHg. Thus, the mean coronary perfusion pressure is less than 70 mmHg. Even a highly sophisticated mechanical device with a duration of compression 50 per cent of cycle time will not produce a mean arterial pressure of 70 mmHg (Taylor *et al.*, 1977). A mean pressure below 70 mmHg is unlikely to be associated with perfusion of ischaemic areas of the myocardium. Thus, progression of myocardial injury may explain the inverse relation between the duration of cardiopulmonary resuscitation and the chance of survival.

Aware of the limitations of cardiopulmonary resuscitation and aiming at the immediate correction of ventricular fibrillation, Pantridge has concentrated on the development of small, inexpensive and, therefore, readily available defibrillators. In the investigation of the miniaturisation of defibrillators and in the quest for a pocket defibrillator, Pantridge considered it imperative to determine whether the 400 watt seconds stored energy currently advocated was necessary. Thus, in 1974, a prospective study of the efficacy of low energy shocks was initiated. Preliminary data indicated that 98 per cent of episodes of ventricular fibrillation might be removed by a delivered energy not greater than 165 watt seconds (Pantridge *et al.*, 1975b).

Animated controversy now exists regarding the energy requirements for successful defibrillation. The majority of workers advocate the use of the maximum stored energy of the defibrillator, usually 400 watt seconds (Green *et al.*, 1971; Dunning, 1972; Standards for Cardiopulmonary Resuscitation (CPR) and Emergency Cardiac Care (ECC), 1974; Benson *et al.*, 1975; Duggan and Barrett, 1975). The maximum energy delivered through a resistance of 50 ohms by most commercially available defibrillators varies from 270 (American Optical) to 330 watt seconds (Pantridge Portable) (Campbell *et al.*, 1977). Workers at Purdue claim that one-third of patients cannot be defibrillated by the conventional devices (Tacker *et al.*, 1974). Tacker *et al.* (1974) state that maximum energy delivered from the usually available defibrillators is inadequate to defibrillate 35 per cent or more of subjects weighing over 50 kg and ineffective in 60 per cent of patients weighing 90 to 100 kg. They, therefore, recommend that defibrillators should be capable of delivering 500 to 1000 watt seconds and presumably storing 600 to 1200 watt seconds (Ewy and Tacker, 1976). These devices would, therefore, be much larger, less portable, more expensive, and less readily available.

The recommendations of Ewy and Tacker (1976) are not supported by the data of other workers (Pantridge *et al.*, 1975a, b; Crampton and Hunter, 1976; Kerber and Sarnat, 1977; Campbell *et al.*, 1977; DeSilva and Lown, 1978). The Belfast data which involved 394 episodes of ventricular fibrillation among 214 patients showed that shocks of 100 watt seconds stored energy were successful in 81 per cent of episodes of ventricular fibrillation (Campbell *et al.*, 1977). A single shock of 100 watt seconds stored energy succeeded in 67 per cent. Shocks of 200 watt seconds stored energy succeeded in 95 per cent and a single shock of 200 watt seconds succeeded in 85 per cent. Body weight was not related to the chance of successful defibrillation with 200 watt seconds stored energy. Among the few patients in the Belfast study who failed to be defibrillated by low energy shocks, there was not a single example of failure with 400 watt seconds stored—the maximal delivered energy was 330 watt seconds. Workers in the University of Virginia obtained similar results. Experience of 11 patients with ventricular fibrillation showed that 100 to 250 watt seconds stored energy consistently removed ventricular fibrillation (Crampton *et al.*, 1977). These workers failed to find a relation between body weight and success of defibrillation. Kerber and Sarnat (1977) were also unable to find such a relation. The lack of a relation between the energy required for defibrillation and the body weight is apparent from other reports. There are many records of successful defibrillation of heavy patients by conventional defibrillators. Ventricular fibrillation complicating acute myocardial infarction was removed in a pregnant woman weighing 108 kg by 1 shock of 300 watt seconds (Curry and Quintana, 1970). Men, weighing respectively 145, 225, and 190 kg, were defibrillated by a single shock of 400 watt seconds stored energy (Lappin, 1974; R. S. Crampton, 1978, personal communication; DeSilva and Lown, 1978).

The views of Tacker *et al.* (1974) are, therefore, directly at odds with those of other observers. This requires explanation. B. Lown and R. A. DeSilva (1978, personal communication to the Editor, *British Heart Journal*) comment that Tacker *et al.* (1974) and Geddes *et al.* (1974),

> '. . . demonstrated that small animals can be defibrillated with less energy than large animals. In these experiments heart weight ranged from 5 gm to 2500 gm or varied by a factor of 500. In adult man, heart weight varies at most by a factor of 4. Other determinants are of more decisive importance, such as the duration of ventricular fibrillation, the cause of fibrillation, whether primary or secondary, the presence and extent of heart disease, the concurrence of metabolic, acid base and electrolyte derangements, electrode position, and no doubt, many other variables. The studies, therefore, have very little bearing on human adult defibrillation.'
>
> 'Tacker *et al.* (1974) also showed in a retrospective study of 111 adults that increasing body weight was associated with decreasing success in defibrillation attempts.'

Lown and DeSilva go on to say,

> 'The authors merely gathered from patient charts the notes of house-officers and correlated success or failure of defibrillation with body weight. Absolutely no information is supplied regarding the several important factors which determine the outcome of cardiac resuscitation. We did a statistical analysis of their data using the Chi-square method. This analysis showed that the relationship between success and failure as a function of body weight in the 111 patients was not significant at a 5 per cent level.'

> 'The same authors also used their retrospectively collected data in 13 patients to plot an energy dosing curve as a function of body weight. A line was drawn between energy requirement in 3 infants, 3 children, and 7 adults, and from this they recommend the dose of energy should be 3·5-6·0 wsec/kg for humans. The data are inadequate for a line to be drawn between the three groups of bunched points and it is neither statistically nor logically valid. Equally disquieting is that these investigators did not employ a homogeneous population and patients differed only as regards one variable under study, namely body weight. The comparison of infants to adults is improper, for the differences between them encompass a multiplicity of cogent factors (other than body weight) which affect the ease of defibrillation.'

The controversy is of considerable importance. Apart from the disadvantages of reduced portability and availability, larger defibrillators carry the risk of cardiac damage. In experiments, increasing the energy of DC shocks was associated with increasing frequency of arrhythmias (Lown *et al.*, 1962; Gold *et al.*, 1977). The higher the energy level, the greater the amount of myocardial damage (DiCola *et al.*, 1976). Clinically, there was a direct relation between the energy used for synchronised DC conversion and the incidence of post-conversion arrhythmias and ST displacement (Resnekov and McDonald, 1967; Lown, 1978).

It has been argued that when the initial shock is of low energy, it may require to be repeated and that 2 low energy shocks cause more damage than a single shock of identical total energy. Animal experiments do not support the latter proposition. When a given amount of energy is delivered by high energy shocks, the resultant myocardial damage is greater than when the same total energy is delivered by twice the number of low energy shocks (Pantridge, 1978).

The Belfast data do not support the proposition that defibrillators should store more than 400 watt seconds. Indeed, the data suggest that this energy level is, for the majority of patients with ventricular fibrillation, grossly excessive. Urging the FDA to prohibit the manufacture of defibrillators storing more than 400 watt seconds, Lown (1978) stated that absence of such action would result in a tragedy greater than the thalidomide catastrophe.

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British Heart Journal, 1978, **40**, 1200-1204

Results of aortocoronary bypass operations
Follow-up in 343 patients

R. M. DONALDSON[1], M. HONEY, M. F. STURRIDGE, J. E. C. WRIGHT, AND R. BALCON

From The London Chest Hospital, London

SUMMARY Three hundred and forty-three patients who had aortocoronary bypass graft operations for disabling angina were followed up for from 6 months to 5 years (average 2 years). 80 per cent had multiple grafts and 20 per cent had additional endarterectomy. The overall mortality within one month of operation was 5 per cent, and in those who had vein graft procedures only was 4 per cent. 11 per cent had a postoperative myocardial infarction (6% perioperative) and there were 3 per cent late deaths. At 3 years 90 per cent are surviving. 80 per cent are asymptomatic without treatment. The mean angina grade was 0·3 at the latest follow-up, compared with 2·5 before operation; maximum exercise tolerance was also significantly improved ($P < 0{\cdot}001$). When angina recurred, it did so in 80 per cent of the cases within 12 months of operation and was usually attributable to inadequate revascularisation. Ventricular function as assessed by preoperative ventriculography was the factor most clearly related to survival rate and the early excellent results of coronary bypass operations seem to be maintained up to 5 years. It is, therefore, reasonable to continue to advise operation if only for relief of angina.

The early excellent clinical results achieved in many centres by aortocoronary bypass grafting has encouraged cardiologists to recommend this operation for symptomatic relief of angina. The continued use of the procedure will depend to a large extent on the late results. In this report we examine our experience with 343 patients followed up for from 6 months to 5 years after operation.

Preoperative assessment

Patients presenting with angina pectoris from February 1971 to February 1976 were considered for surgical treatment and admitted to hospital for evaluation. The preoperative assessment and operative procedure have been described previously (Balcon *et al.*, 1974). Because of chest pain, 893 patients were investigated angiographically. This excludes those that had associated valvar disease or non-coronary myocardiopathies. There were 343 patients who were referred for an aortocoronary bypass graft operation, and 304 of these were men and 39 women, with ages ranging from 19 to 71 years (median 50). Seventy-five per cent (75%) of the patients were between 40 and 60 years of age.

Angina was graded from 1 to 4 using the same criteria as the New York Heart Association grading for dyspnoea. The average angina grade was 2·5; the duration of angina ranged from 1 week to 19 years and averaged 20 months. Ninety-six (28%) had exertional dyspnoea as a limiting symptom in addition to angina and in those patients the mean dyspnoea grade was 2·1. Ninety per cent (90%) of the patients had been treated with sublingual glyceryl trinitrate and 85 per cent with beta-adrenergic blocking agents. Of the patients 240 (70%) had abnormal resting electrocardiograms and 50 per cent had electrocardiographic evidence of at least one previous myocardial infarction.

The patients usually performed a standardised exercise test in the upright position on a bicycle ergometer with recording of a bipolar chest lead, starting at 24·5 Watts (150 kpm/m) and increasing by increments of 24·5 Watts (150 kpm/m) every 2 minutes until forced to stop by the development of angina, 2 mm ST segment depression on the electrocardiogram, dyspnoea, or fatigue. Two

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hundred and seventy-seven patients had an exercise test before and after operation; the maximum work load preoperatively ranged from 24·5 Watts (150 kpm/m) to 171·7 Watts (1050 kpm/m), with an average of 85·8 Watts (525 kpm/m).

Left and right heart catheterisation was performed from the right arm after premedication with 20 to 25 mg of intramuscular diazepam. Left ventriculography was performed in the right anterior oblique projection and followed by selective coronary angiography in multiple projections, preferably using the Sones technique. A caesium iodide image intensifier was used and 35 mm cine film was exposed at 35 frames per second. The angiographic severity of coronary artery disease was represented by a numerical score. Each major vessel was scored on a scale of 0 to 4; 0 was normal, 4 total occlusion, and 1 to 3, stenosis of increasing severity. Patients selected for bypass surgery were those who had angiographic demonstration of major (grade 3 or 4) lesions obstructing one or more of the main coronary arterial branches and who continued to have angina, interfering with their normal activities in spite of treatment with glyceryl trinitrate and beta-adrenergic blocking agents. Fifty-five (16%) patients had major lesions (score 3 or 4) of a single vessel, 127 (37%) of 2, and 161 (47%) of 3 vessels. Nineteen (6%) had a major lesion (i.e. grade 3 or 4) of the left main coronary artery.

The systolic movement of the myocardium was analysed in each of 3 segments (anterior, apical, and posteroinferior) of the outline of the left ventricle on the ventriculogram, and was classed either as normal or as showing akinetic or dyskinetic (paradoxical) wall motion (Herman and Gorlin, 1969). Areas of reduced wall movement (hypokinesis), which often improved after sublingual glyceryl trinitrate, were classified as normal. Thus the 'normal' group included some patients with reduced ejection fraction. Those with severe left ventricular dysfunction (i.e. 3 hypokinetic segments and greatly reduced ejection fraction) were excluded. The left ventriculogram was 'normal' in 246 patients (72%); 64 (19%) had 1 akinetic or dyskinetic segment; and 33 (10%) had 2 or more abnormally contracting segments on ventriculography.

Operative procedure

Operation was usually performed within one month of investigation. After removal of a length of saphenous vein, the coronary anastomoses were performed under normothermic cardiopulmonary bypass with intermittent aortic cross-clamping. During the past 3 years, endarterectomy has been done before graft insertion in some patients; others had additional procedures related to their coronary artery disease. One-fifth of the patients had grafts to a single vessel only. The remainder had multiple graft operations (44% double grafts, 31% triple, and 6% quadruple grafts). A prior endarterectomy was necessary to render a vessel suitable for grafting in 20 per cent of the patients. In 29 patients (9%) bypass grafting was combined with other procedures, viz. left ventricular aneurysmectomy in 18 (5%), closure of ventricular septal defect in 6 (2%), and mitral annuloplasty in 5 (2%). Most patients were discharged from hospital by the end of the second week and anticoagulant treatment was continued for at least 3 months after operation.

The mortality within one month of operation was 5 per cent (18 patients) but for those who underwent an uncomplicated bypass graft procedure only this figure was 4 per cent (13 patients). Eleven patients died in hospital: 4 from pulmonary embolism (3 of these before routine postoperative anticoagulant treatment was used), 1 from haemorrhage, 2 from respiratory complications, 1 from unheralded ventricular fibrillation, and 3 who could not be weaned from cardiopulmonary bypass from myocardial failure.

The diagnosis of perioperative myocardial infarction was based on electrocardiographic evidence: the appearance of new Q waves, bundle-branch block, or loss of R wave progression in praecordial leads. This was documented in 20 patients (6%).

Analysis of data

Data were recorded on mark-sense cards, stored, and then analysed on a CDC 6400 computer. Life table analysis was performed to determine the survival rates, and differences in survival rate between subgroups were tested for statistical significance using the chi-square test (χ^2).

Postoperative follow-up

Patients were seen at 6-monthly intervals after operation, usually at a special follow-up clinic, where the occurrence of dyspnoea, angina, or myocardial infarction, and results of exercise testing were documented. In some patients this information was obtained from the referring physician. Of the 325 survivors of operation, 315 (97%) were included in the follow-up, which ranged from 6 months to 5 years, with an average of 2 years. Ten (3%) of the patients were either untraceable or overseas and lost to follow-up.

There were 11 late deaths (3% of all cases) from cardiac causes, including 5 that were sudden (overall mortality 8%). Fifteen patients (5%) have had a documented late myocardial infarction and 5 of these patients died. Two hundred and sixty-one patients (80%) had no further angina after operation and required no antianginal treatment. In a further 18 (6%) angina was improved by at least two clinical grades; 38 (12%) were either unchanged or worse after operation. The average grade of angina has fallen from 2·5 to 0·3 ($P < 0{\cdot}001$). When angina reappeared after operation, it did so in 48 (86%) of the 56 patients within 12 months of operation and only 8 (3%) of all survivors had late recurrence of angina (2 or more years after operation). In the 277 patients who performed bicycle ergometer tests before and after operation, the exercise tolerance was significantly greater in the postoperative tests [from average of 85·8 Watts (525 kpm/m) to 106 Watts (648 kpm/m)] ($P < 0{\cdot}001$) and angina was the limiting factor in only 69 patients (25%). Of our patients 125 (36%) have been reinvestigated by coronary arteriography and in these 79 per cent of the 243 grafts were patent at an average of 14 months after operation.

The overall 3-year survival rate was 90·4 per cent. There was a significant difference between the survival of the patients with normal left ventricular function and that of the group with impaired ventricular contractility. Of the former 80 per cent survived 3 years, compared with a 63 per cent and 35 per cent survival for those with one and two (or more) akinetic or dyskinetic segments, respectively (Fig.).

Discussion

The reported hospital mortality in large series for bypass grafting alone varies from 0·7 per cent (Ullyot *et al.*, 1975) to 7 per cent (Anderson *et al.*, 1974). Our figure of 4 per cent is comparable. The excellent symptomatic relief that follows bypass graft surgery had been previously documented and clinical improvement can be expected in 80 to 90 per cent of the patients. The presence of disabling symptoms constituted the prime indication for operation in our cases and 80 per cent of the patients who survived operation are currently asymptomatic without drug treatment. Similar results have been obtained by others (Manley and Johnson, 1972; Kouchoukos *et al.*, 1974; Ross, 1975; Sheldon *et al.*, 1975). In our patients bypass graft surgery was also evaluated by exercise testing, which showed a significant improvement in maximal work capacity, as in other comparable series (Amsterdam *et al.*, 1970; Lapin *et al.*, 1973). This has also been shown by Siegel *et al.* (1974) in patients in whom only partial myocardial revascularisation was achieved. Perhaps more important, stress induced angina occurred significantly less often in the postoperative exercise test. The considerable symptomatic improvement was maintained throughout the 5-year follow-up period, as in the large group of patients reported from the Cleveland Clinic by Sheldon *et al.* (1975).

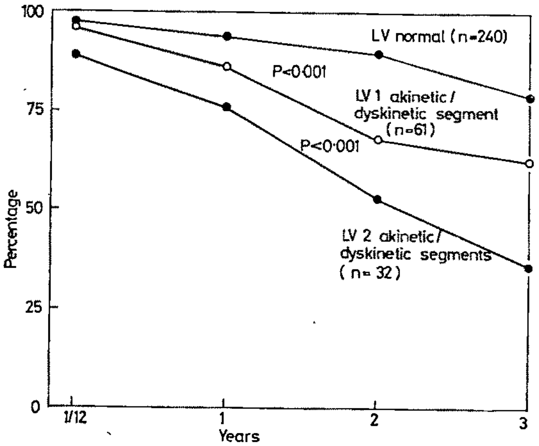

Fig. *Postoperative survival curves for individual ventriculographic categories.*

When angina recurred, it did so in 86 per cent of 56 cases within 12 months of operation during the time when graft occlusion is also most likely to occur (Flemma *et al.*, 1972). Most clinical studies have shown a close correlation between bypass graft patency and good symptomatic result (Adam *et al.*, 1972; Manley and Johnson, 1972). We also have observed that early reappearance of symptoms was associated with non-functioning grafts or inadequate revascularisation (Banim and Balcon, 1976). The proportion of patients receiving multiple grafts has increased since our last report (Balcon *et al.*, 1974) from 56 to 80 per cent, and it is our current view that revascularisation should be as complete as possible, as this appears to be the most important factor in determining the degree of symptomatic improvement. Endarterectomy was done in 20 per cent of the patients in addition to bypass grafting to achieve maximal revascularisation; as we have found that this does not adversely affect the clinical result, we now do this wherever necessary (Banim *et al.*, 1976). Bypass grafting can be safely combined with aneurysmectomy in the treatment of post-infarction ventricular aneurysms (Donaldson *et al.*, 1976). All but 1 of the 18 patients in this series who underwent the combined procedure had excellent symptomatic relief.

Postoperative transmural infarction diagnosed by electrocardiographic criteria has been reported to occur in between 1·2 per cent (Cannon *et al.*, 1974) and 20 per cent (Brewer *et al.*, 1973). The 6 per cent perioperative infarction rate in our group is similar to that reported by Sheldon *et al.* (1975). Detailed analysis of wall motion abnormalities suggests that these figures may underestimate the true incidence (Rickards *et al.*, 1977). Fifteen patients had myocardial infarction during the follow-up period; all had recurrent angina before this occurred.

It seems unlikely that perioperative infarction alone can account for all the symptomatic improvement seen after operation, since this occurred in only a small proportion of those who improved. It has also been suggested that the relief of pain can be attributed to denervation of the ischaemic zone (Soloff, 1973) or to a non-specific effect of surgery (Diamond *et al.*, 1960). However, the close correlation between graft patency and clinical benefit suggests that these mechanisms are unlikely to be responsible for the improvement which follows operation in more than a small proportion of patients.

Two-year survival for our group was 93 per cent and is similar to that reported from large surgical centres which ranges from 85 per cent (McNeer *et al.*, 1974) to 94 per cent (Sheldon *et al.*, 1975). Left ventricular function as estimated by preoperative ventriculography appears to be an important determinant of prognosis in patients treated medically (Oberman *et al.*, 1972; Bruschke *et al.*, 1973; Burggraff and Parker, 1975). Of our patients, 28 per cent had one or more akinetic or dyskinetic segments on the ventriculogram, and we have found that ventricular function assessed in this way was also the most important predictor of survival after operation; Sheldon *et al.* (1975) have made a similar observation. The extent of myocardial damage was most probably underestimated in our group of patients as 70 per cent of the patients had abnormal resting electrocardiograms and 50 per cent had at least one previous myocardial infarction; furthermore, lesser abnormalities (hypokinesis) in segmental myocardial contractility were not taken into consideration.

Our experience shows that the excellent early results of aortocoronary bypass operation are maintained over a period of up to 5 years; it is, therefore, reasonable to continue to advise operation if only for relief of angina without taking into consideration any improved prospects of survival which may have resulted.

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Haemodynamics during maximal exercise after coronary bypass surgery

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SUMMARY Fifty patients underwent an objective measurement of physical working capacity by means of a multistage test of maximally tolerated exertion before and after coronary bypass surgery; 29 patients also had haemodynamic measurements during maximal exercise before and after coronary bypass surgery. The patients were divided into 3 groups according to the degree of revascularisation: adequate ($n = 20$), partial ($n = 17$), or none ($n = 13$).

Adequate revascularisation induces a large increase in physical working capacity because of an increased maximal heart rate and maximal cardiac output; stroke volume during maximal exercise and ejection fraction at rest were not modified, suggesting no major changes in left ventricular function. After unsuccessful coronary bypass surgery, the physical working capacity was unchanged despite an increased maximal heart rate; maximal cardiac output was unchanged and stroke volume during maximal exercise was significantly lower. These undesirable results are often associated with perioperative myocardial infarction and are attended by a decreased ejection fraction at rest; these data suggest an impaired left ventricular function after unsuccessful coronary bypass surgery. The results of partial revascularisation are intermediate but appear to be determined by the incidence of partial graft failure which is also often associated with perioperative myocardial infarction.

From individual changes in data collected during maximal exercise testing, it is often impossible to predict the degree of revascularisation.

Aortocoronary bypass surgery improves or relieves angina pectoris in 60 to 90 per cent of the patients (Ross, 1975). These figures are most often based on a purely clinical evaluation and only a few reports include objective assessment of the physical working capacity, that is pre- and postoperative maximal exercise tests (Bartel *et al.*, 1973; Guiney *et al.*, 1973; Lapin *et al.*, 1973; Balcon *et al.*, 1974; Knoebel *et al.*, 1974; Frick *et al.*, 1975; Merrill *et al.*, 1975; Siegel and Loop, 1976).

The effects of coronary bypass surgery on the haemodynamic response to exercise largely remain to be established since the few available studies include only data collected during mild exercise (Rutherford *et al.*, 1972; Campeau *et al.*, 1974; Barry *et al.*, 1976) or they do not enable one to relate the observed changes to the graft status (McDonough *et al.*, 1974).

The purposes of the present study were to correlate the changes in physical working capacity after coronary bypass surgery with the degree of revascularisation and to determine the haemodynamic modifications underlying these changes. It involved direct measurement of the physical working capacity by maximal exercise testing together with selective coronary arteriography and left ventriculography before and 3 months after coronary bypass surgery. A wide subset of patients (29/50) also had haemodynamic measurements during maximally tolerated exertion before and after coronary bypass surgery.

Subjects

Fifty patients (46 men and 4 women) were included in this study. They underwent a coronary bypass surgical procedure for the treatment of severe angina pectoris refractory to medical treatment. Before operation, they had no clinical signs of heart failure and their preoperative ejection fraction was above 50 per cent. Eleven patients had electrocardiographic signs of healed myocardial infarction before

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operation. The study group was selected from 252 operated patients who had undergone an objective assessment of graft status 3 months after operation. From these 252 patients, 103 had preoperative exercise studies and these exercise studies were repeated 3 months after operation in only 50 patients who constitute the material of the present study. The major reasons for not repeating the exercise studies 3 months after operation in 53 patients were the excellent subjective results which were considered by the referring physician as sufficient evidence for surgical success. Patients with doubtful or poor subjective results are, therefore, over-represented; this accounts for the low graft patency rate (62%) observed in the present group, contrasting with the 79 per cent patency rate observed in our total group of 252 patients (up to November 1976).

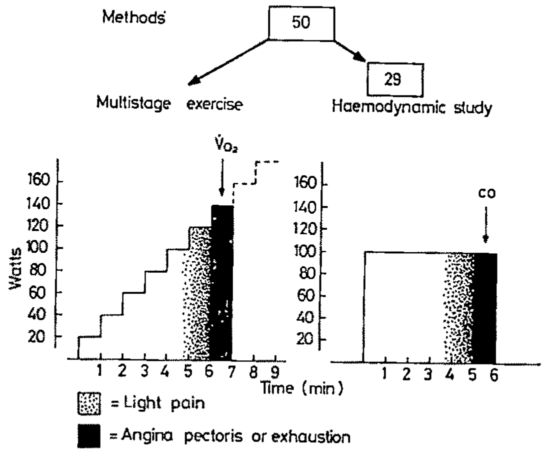

Fig. 1 *Procedure of the study.*

Methods

The methods for maximal exercise testing were as previously reported (Rousseau *et al.*, 1973; Detry *et al.*, 1975). Briefly, a few days before the pre- and postoperative arteriographic study all patients performed a multistage uninterrupted test of maximal exercise on a bicycle ergometer in order to measure their physical working capacity, that is the oxygen consumption at maximally tolerated exercise ($\dot{V}_{O_2}$SL $\dot{V}_{O_2}$ max) and the maximal heart rate (HR). The initial workload was 20 watts for 1 minute and the intensity of the exercise was then increased every minute by 20 watts: the exercise test was continued until typical angina pectoris developed or until subjective exhaustion. The electrocardiogram was recorded on paper at 1 minute intervals and it was visually analysed; the horizontal or downsloping depression of the ST segment was measured at the J point with the intersection of the PR interval with the QRS as zero voltage reference. The methods for collecting expiratory gases and measuring oxygen consumption were previously reported (Detry *et al.*, 1972). Beta-blocking agents were discontinued at least 48 hours before the exercise test and no patient was on digitalis therapy. The results of this non-invasive exercise test were used to select the workloads to be used during the haemodynamic study (Fig. 1).

The procedure for the preoperative haemodynamic study in 26 patients included haemodynamic measurements during exercise-induced angina pectoris; the workload corresponding to the anginal level was selected so as to precipitate angina pectoris after 4 to 5 minutes. In 3 additional patients, angina pectoris could not be precipitated by exercise before operation and the maximal workload was interrupted for dyspnoea and fatigue. Depending on the results of the exercise test, the postoperative maximal workload used for the haemodynamic study was either lower, the same, or greater than the preoperative one; it induced angina pectoris in 6 patients and corresponded to subjective exhaustion without angina pectoris in the remaining 23 patients.

The cardiac output was measured in the sitting position during the last minute of the maximal workload using the Fick principle. The catheters were introduced percutaneously as described previously, and the blood oxygen content was measured with the Lex-O_2-CON analyser (Clerbaux *et al.*, 1973). The pressure-rate product was calculated as the product of heart rate and mean brachial artery pressure.

Coronary arteriography was performed by the femoral route using the method of Bourassa (Lesperance *et al.*, 1970). The coronary arteriograms and the selective injections of the grafts were always preceded by left ventriculography in the right

Table 1 *Clinical and angiographic data*

	Revascularisation		
	Adequate (*n* = *20*)	*Partial* (*n* = *17*)	*No* (*n* = *13*)
Age	50	50	48
Number of diseased vessels	2·0	2·5	2·3
Number of grafts	28	28	18
Status of the graft:			
Patent	28	18	—
Occluded	—	10	18
Myocardial infarction (ECG):			
Preop	7	2	2
Postop	7	7	8

anterior oblique position. The films were reviewed independently by 2 separate investigators. The coronary lesions and status of the grafts were scored according to the recommendations of the American Heart Association (Austen *et al.*, 1975). The left ventricular ejection fraction was calculated using the area-length method: postectopic beats were disregarded.

The patients received 74 saphenous vein grafts; 27 patients had a single graft, 22 a double graft, and 1 a triple graft. The patients have been divided in 3 groups according to the degree of revascularisation which was determined as follows (Table 1).

Adequate revascularisation (group 1; n = 20; 28 grafts): all artery with stenoses ⩾ 50 per cent were successfully grafted. Ten patients with a complete obstruction of 1 (n = 9) or 2 (n = 1) coronary artery are included in this group; the distal portion of these obstructed arteries was not visualised at preoperative arteriography, and endarterectomy was never attempted.

Partial revascularisation (group 2; n = 17; 28 grafts): partial graft failure (n = 10; 20 grafts) or some stenotic coronary lesions not bypassed because of the poor condition of the distal artery (n = 7; 8 grafts).

No revascularisation (group 3; n = 13; 18 grafts): total graft failure.

Evidence of peri- or postoperative myocardial infarction was based only on the development of new pathological Q waves (Assad-Morell *et al.*, 1975).

Statistical analysis of the data was done using the paired t test of Student.

Informed consent was obtained from each patient and no complications occurred as a result of the experimental procedure.

Results

By definition, the patency rate was 100 per cent in group 1 and 0 per cent in group 3; in group 2, 64 per cent of the grafts were patent after operation (Table 1). After coronary bypass surgery, postoperative myocardial infarctions were never observed in group 1 but they were present in 46 per cent (6/13) of the patients of group 3 and in 29 per cent (5/17) of the patients of group 2; all patients of group 2 with postoperative myocardial infarction had partial graft failure. From these 11 postoperative myocardial infarctions, 9 were in the myocardial zone supplied by a grafted artery (8 occluded grafts and 1 patent graft) and 2 were in a myocardial zone supplied by a diseased ungrafted artery.

All individual data are listed in Table 2 which also presents for each group and subgroup the mean values of the data collected during maximal exercise testing. The changes in physical working capacity are clearly related to the degree of revascularisation since physical working capacity increased by 47 per cent in group 1, 23 per cent in group 2, and was not significantly modified in group 3; similar increases in the maximal heart rate were, however, noted in the 3 groups. After coronary bypass surgery, angina pectoris at maximal exercise disappeared in 83 and 87 per cent of the patients of group 1 and 2 but 58 per cent of the patients of group 3 were no longer limited by angina after unsuccessful surgery. Electrocardiographic signs of myocardial ischaemia during maximal exercise were significantly reduced in groups 1 and 2 and unmodified in group 3. Finally, the ejection fraction measured at rest was significantly lower after surgery in group 3.

Haemodynamic data at the maximal exercise level are available in 3 subsets of patients whose changes in $\dot{V}_{O_2}$ max, maximal heart rate, angina pectoris, and ejection fraction were similar to those observed in the 3 groups of patients (Table 2). The 50 per cent greater $\dot{V}_{O_2}$ max in group 1 resulted from significant increases in maximal heart rate (+ 28%) and maximal cardiac output (+ 35%) without modification of the stroke volume during maximal exercise; simultaneously, the pressure-rate product increased by 43 per cent while the $(AV)O_2$ difference reached normal maximal values. The data collected in the 10 patients of group 1 with an ungrafted occluded coronary artery were similar to those obtained in the other patients of group 1. In group 3, the unchanged $\dot{V}_{O_2}$ max was attended by a slight decrease in the maximal cardiac output despite a 15 per cent increase in maximal heart rate; the stroke volume during maximal exercise was 18 per cent lower after operation in this group while the ejection fraction was 12 per cent lower. Intermediate changes were noted in group 2.

From the individual changes in stroke volume during maximal exercise (Fig. 2) it is apparent that the most striking decreases in stroke volume were observed in patients with a postoperative myocardial infarct. After coronary bypass surgery, in group 3, the stroke volume was 22 per cent lower (from 90 to 70 ml) in the 4 patients with postoperative myocardial infarction and 15 per cent lower (from 81 to 69 ml) in the 5 patients without electrocardiographic signs of postoperative myocardial infarction.

Since graft failure and incidence of postoperative myocardial infarction appear to determine the changes in physical working capacity, the 17 patients in group 2 have been further subdivided into 2 smaller groups: those with incomplete surgery and

Table 2 *Individual data*

No.		*Sex*	*Age*	*Myocardial infarction* (*ECG*)	*Coronary arteriography*				*Ejection fraction* (%)
					LM	*LAD*	*Circ.*	*RCA*	
Group 1: Adequate revascularisation									
1	Pre	M	48	—	—	90	—	—	88
	Post			—	—	P_o	—	—	94
2	Pre	M	62	—	—	90	90	100	69
	Post			—	—	P_o	P_o	—	59
3	Pre	M	31	Inf.	—	—	100	90	50
	Post			Inf.	—	—	—	P_o	41
4	Pre	M	51	—	—	—	—	75	78
	Post			—	—	—	—	P_o	65
5	Pre	M	45	Inf.	—	90	75	100	62
	Post			Inf.	—	P_o	P_o	—	72
6	Pre	M	47	Inf.	—	90	—	100	51
	Post			Inf.	—	P_o	—	—	57
7	Pre	M	51	—	—	90	—	—	64
	Post			—	—	P_o	—	—	76
8	Pre	M	47	Inf.	—	90	—	100	51
	Post			Inf.	—	P_o	—	—	60
9	Pre	M	60	—	—	75	90	90	70
	Post			—	—	P_o	P_o	P_o	79
10	Pre	F	43	—	—	—	—	90	76
	Post			—	—	—	—	P_o	79
11	Pre	M	46	—	—	90	—	100	65
	Post			—	—	P_o	—	—	66
Mean 1-11	Pre		48						66
	Post								68
	%								+ 4
	P								NS
12	Pre	M	51	Inf.	—	75	75	100	61
	Post			Inf.	—	P_o	P_o	—	58
13	Pre	M	65	—	—	75	90	100	82
	Post			—	—	P_o	P_p	—	61
14	Pre	M	44	—	—	90	75	100	62
	Post			—	—	P_p	P_o	—	63
15	Pre	M	48	—	—	90	—	—	76
	Post			—	—	P_o	—	—	68
16	Pre	M	51	Inf.	—	90	100	100	58
	Post			Inf.	—	P_p	—	—	53
17	Pre	M	46	—	—	90	—	—	60
	Post			—	—	P_o	—	—	66
18	Pre	F	52	—	—	50	—	—	87
	Post			—	—	P_p	—	—	87
19	Pre	M	49	Inf.	—	90	—	90	57
	Post			Inf.	—	P_o	—	P_o	71
20	Pre	M	54	—	—	—	—	70	63
	Post			—	—	—	—	P_o	50
Mean 1-20	Pre		50						66
	Post								66
	%								—
	P								NS
Group 2: Partial revascularisation									
21	Pre	M	55	—	90	75	75	100	77
	Post			—	—	O_p	P_p	—	50
22	Pre	M	41	—	90	—	75	50	58
	Post			Lat.	—	P_o	O_o	—	54
23	Pre	M	53	Inf.	—	90	—	50	87
	Post			Inf.	—	P_o	—	—	87
24	Pre	M	63	Inf.	—	75	100	75	66
	Post			Inf.	—	P_p	—	O_p	66
25	Pre	M	51	—	—	90	—	75	70
	Post			—	—	P_p	—	—	77
26	Pre	M	46	—	—	90	—	50	59
	Post			—	—	P_o	—	—	70
27	Pre	M	44	—	90	90	90	—	60
	Post			Inf.	—	P_p	O_o	—	44
28	Pre	M	53	—	—	75	—	90	58
	Post			Inf.	—	P_p	—	O_o	41
29	Pre	M	39	—	—	90	—	50	74
	Post			—	—	P_p	—	—	80
Mean 21-29	Pre		49						68
	Post								63
	%								−7
	P								NS

orkload *vatts)*	*Angina*	*Data during maximally tolerated exercise*						
		ST depression (*mm*)	$\dot{V}O_2$ (*l/min*)	*HR* (*beats/min*)	*SV* (*ml/beat*)	*CO* (*l/min*)	*HR* × $\overline{BP}$ (*mmHg/min*$^{-2}$)	$\overline{P}_{AP}$ (*mmHg*)
100	Yes	−2·5	1·35	126	75	9·4	176	40
170	No	—	2·06	158	80	12·6	265	30
40	Yes	—	0·72	85	89	7·6	82	24
120	No	−3·0	1·39	147	73	10·7	194	31
160	Yes	—	2·07	176	79	14·0	246	48
160	No	—	1·79	175	65	11·7	226	40
150	No	−1·0	1·75	148	80	11·8	178	24
150	No	−0·5	1·76	124	110	13·7	145	27
50	Yes	−2·0	0·89	101	76	7·7	109	27
150	No	—	1·82	160	88	14·1	230	30
90	Yes	−2·0	1·10	132	58	7·6	211	52
150	No	—	1·80	162	72	11·7	143	33
70	Yes	−1·5	1·11	134	79	10·6	204	28
130	No	−2·2	1·54	168	80	13·4	228	33
75	Yes	−1·0	1·01	114	66	7·5	128	39
125	Yes	−1·2	1·88	166	76	12·7	229	34
20	Yes	−4·5	0·38	96	78	7·5	155	22
170	No	—	1·84	177	78	13·9	276	40
100	Yes	−1·0	1·24	138	72	10·0	163	24
100	No	−0·7	1·27	157	74	11·6	195	27
75	Yes	−1·5	1·03	126	72	9·0	164	30
140	No	−1·5	1·83	163	67	11·9	248	34
84	10	−1·5	1·15	125	75	9·3	155	32
.42	1	−0·8	1·73	160	78	12·6	221	33
69	−90	−47	+50	+28	+4	+35	+43	—
0·005	—	NS	0·005	0·005	NS	0·005	0·01	NS
40	Yes	−3·0	1·60	130				
60	No	—	1·80	180				
00	Yes	−2·0	1·20	103				
60	No	—	1·80	142				
00	Yes	−2·5	1·30	155				
20	No	—	2·40	175				
00	Yes	−2·0	1·09	118				
20	No	−2·2	2·46	185				
40	Yes	−1·0	1·40	120				
60	No	−2·0	1·30	165				
10	Yes	−2·5	1·30	147				
85	No	−1·2	1·78	150				
20	Yes	−2·0	0·95	160				
90	Yes	−1·5	0·94	155				
00	Yes	−3·0	1·06	120				
00	No	−2·5	2·07	152				
50	No	−1·5	1·39	160				
50	No	−1·0	1·77	180				
00	18	−1·8	1·20	129				
56	3	−1·0	1·77	162				
56	83	−44	+47	+25				
0·001	—	0·05	0·001	0·001				
50	Yes	−5·0	0·92	112	63	7·1	126	38
90	Yes	−3·0	1·23	142	70	9·9	171	37
00	Yes	−3·5	1·36	130	81	10·5	182	58
00	No	—	2·42	178	84	14·9	256	48
00	Yes	−2·0	1·29	151	63	9·6	211	35
50	No	−0·5	1·84	164	83	13·7	236	32
50	Yes	−4·5	1·94	152	84	12·7	195	50
50	No	—	1·89	162	92	14·9	209	21
75	Yes	—	0·93	68	97	6·6	79	40
70	No	−1·0	2·04	155	88	13·6	205	38
50	Yes	−2·2	1·10	118	86	10·2	149	48
45	No	—	2·38	176	77	13·5	211	35
00	Yes	−3·0	1·24	141	65	9·2	180	42
50	Yes	−1·0	0·79	152	37	5·6	188	46
00	Yes	—	1·29	108	95	10·3	134	29
50	No	—	1·47	168	58	9·7	215	37
30	No	—	2·29	179	92	16·5	226	25
30	No	—	2·34	180	91	16·4	220	30
01	8	−2·2	1·37	129	81	10·3	166	41
47	2	−0·6	1·82	164	76	12·5	220	36
6	75	−73	+33	+27	−6	+21	+33	−12
0·05	—	0·02	NS*	0·01	NS	NS*	0·01	NS

Table 2 *Individual data—continued*

No.		*Sex*	*Age*	*Myocardial infarction* (*ECG*)	*Coronary arteriography*				*Ejectio fractio* (%)
					LM	*LAD*	*Circ.*	*RCA*	
30	Pre	M	53	—	—	90	50	75	66
	Post			—	—	O_o	—	P_o	74
31	Pre	M	49	—	—	90	75	100	70
	Post				—	O_p	—	P_p	65
32	Pre	M	42	—	—	90	75	90	59
	Post			Inf.	—	O_p	—	P_o	52
33	Pre	M	44	—	—	90	90	—	76
	Post			—	—	P_o	—	—	72
34	Pre	M	64	—	75	75	—	90	77
	Post			AS	—	O_p	—	P_o	50
35	Pre	M	54	—	—	90	90	50	77
	Post			—	—	P_o	O_p	—	80
36	Pre	M	50	—	—	—	75	90	73
	Post			—	—	—	—	P_o	83
37	Pre	M	49	—	—	90	75	75	79
	Post			—	—	P_o	—	P_o	67
Mean 21-37	Pre		50						70
	Post								65
	%								−6
	P								NS
Group 3: No revascularisation									
38	Pre	M	45	—	—	50	75	75	72
	Post			—	—	O_o	—	O_p	63
39	Pre	M	52	—	75	75	—	75	53
	Post			—	—	O_o	O_o	—	49
40	Pre	M	39	Inf.	—	90	50	100	57
	Post			Inf.	—	O_o	—	—	44
41	Pre	F	61	—	—	90	90	100	79
	Post			—	—	O_o	—	—	63
42	Pre	M	39	Inf.	—	50	75	100	66
	Post			Inf.	—	O_o	—	—	74
43	Pre	M	53	—	—	75	75	100	72
	Post			Inf.	—	O_p	O_p	—	48
44	Pre	M	47	—	—	90	—	—	76
	Post			Ant.	—	O_p	—	—	80
45	Pre	M	47	—	—	90	—	—	87
	Post			AS	—	O_o	—	—	89
46	Pre	M	48	—	—	90	—	—	84
	Post			AS	—	O_o	—	—	60
Mean 38-46	Pre		48						72
	Post								64
	%								−12
	P								NS*
47	Pre	F	39	—	50	75	—	—	67
	Post			—	—	O_o	—	—	77
48	Pre	M	48	—	—	90	—	—	79
	Post			Ant.	—	O_o	—	—	44
49	Pre	M	58	—	—	50	90	90	61
	Post			—	—	—	O_p	O_o	64
50	Pre	M	48	—	—	90	75	75	85
	Post			Ant.	—	O_o	—	O_p	66
Mean 38-50	Pre		48						72
	Post								63
	%								−12
	P								0·05

Abbreviations: M, male; F, female; Inf., inferior; Ant., anterior; AS, anteroseptal; Lat., lateral; LM, left main coronary artery; LAD, left an descending artery; Circ., circumflex artery; RCA, right coronary artery; P, patent graft; O, occluded graft; P_o, O_o, occlusion of the proximal ste P_p, O_p, patency of the proximal stenosis; $\dot{V}O_2$, oxygen consumption; HR, heart rate; SV, stroke volume; CO, cardiac output; $\overline{BP}$, mean brachial pressure; $\overline{P_{AP}}$, mean pulmonary artery pressure; NS*, $0·05 < P < 0·10$.

load	*Angina*	*Data during maximally tolerated exercise*						
)		*ST depression* (*mm*)	$\dot{V}O_2$ (*l/min*)	*HR* (*beats/min*)	*SV* (*ml/beat*)	*CO* (*l/min*)	*HR* × $\overline{BP}$ (*mmHg/min*$^{-2}$)	$\overline{P_{AP}}$ (*mmHg*)
	Yes	−1·0	1·89	168				
	No	—	1·74	170				
	Yes	−4·0	1·64	136				
	No	−4·0	2·02	175				
	Yes	−0·7	1·29	133				
	No	−2·0	1·50	170				
	Yes	−6·0	1·85	153				
	No	−0·5	2·74	180				
	Yes	−2·0	1·47	115				
	No	−1·7	1·52	138				
	Yes	−2·7	1·84	180				
	No	−1·5	1·93	170				
	No	−2·5	1·90	145				
	No	—	1·97	175				
	Yes	−3·0	1·34	130				
	No	−3·5	1·64	180				
	15	−2·5	1·50	136				
	2	−1·1	1·85	167				
	87	−56	+23	+22				
05	—	0·01	0·01	0·001				
	Yes	−2·0	2·24	140	110	15·4	179	23
	Yes	−2·0	1·53	140	85	11·9	213	36
	Yes	−2·5	1·63	158	75	11·9	202	30
	Yes	−3·5	1·49	179	59	10·6	240	26
	Yes	—	1·26	138	68	9·3	185	24
	No	−1·0	1·36	110	65	7·2	152	32
	Yes	−3·0	0·89	108	63	6·8	97	24
	Yes	−1·5	1·09	144	59	8·5	115	27
	No	−1·0	2·51	168	88	14·7	242	37
	No	—	2·29	178	80	14·3	263	36
	Yes	−2·0	1·07	120	66	7·9	163	54
	No	—	1·49	163	50	8·1	196	59
	Yes	−2·0	1·51	120	113	13·6	122	23
	No	—	2·18	167	84	14·0	240	30
	Yes	+2·0	1·43	132	85	11·2	158	30
	No	+2·0	2·11	168	78	13·2	242	24
	Yes	−1·5	2·06	158	98	15·6	177	30
	No	—	2·05	184	74	13·7	217	31
	8	−1·7	1·62	138	85	11·8	169	31
	3	−0·7	1·73	159	70	11·3	209	34
	62	−59	+7	+15	−18	−4	+24	+10
	—	NS	NS	0·05	0·005	NS	0·02	NS
	Yes	−1·0	1·00	132				
	No	—	1·28	145				
	Yes	−1·0	0·99	94				
	Yes	−2·0	1·17	142				
	Yes	−7·0	2·14	150				
	No	−8·0	2·16	163				
	Yes	−2·2	1·10	92				
	Yes	−2·7	1·14	128				
	12	−1·8	1·52	131				
	5	−1·4	1·64	154				
	58	−19	+8	+18				
	—	NS	NS	0·005				

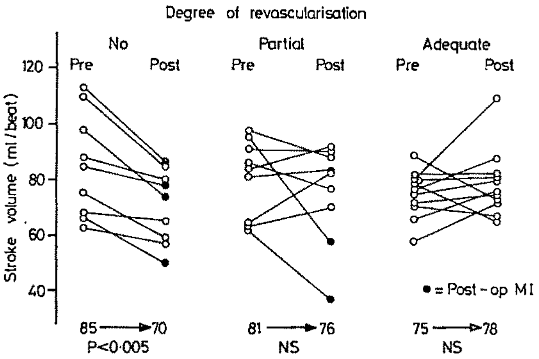

Fig. 2 *Individual changes in stroke volume during maximally tolerated exercise after coronary bypass surgery.*

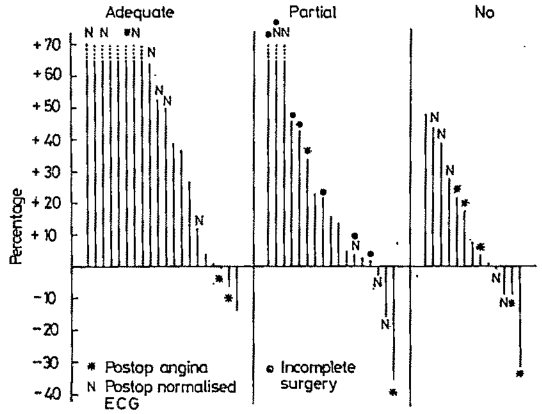

Fig. 3 *Individual changes in physical working capacity ($\dot{V}_{O_2}$ max or $\dot{V}_{O_2}SL$) after coronary bypass surgery.*

those with partial graft failure (Table 3). Though the number of patients in each subgroup is small, these data suggest that the effects of partial graft failure are similar to those of total graft failure while the results of incomplete surgery look similar to those of adequate revascularisation.

From the individual changes in physical working capacity, it was not easy to predict the degree of revascularisation (Fig. 3); all 14 patients with a 50 per cent or larger increase in $\dot{V}_{O_2}$ max had adequate (11) or partial (3) revascularisation, while among the 19 patients with less than a 10 per cent increase in $\dot{V}_{O_2}$ max, 12 had adequate or partial revascularisation and 7 had no revascularisation. Allowing for the complete normalisation of the exertional electrocardiogram and the persistence of exertional angina pectoris we could not give a better prediction of the degree of revascularisation. The overlap between the groups was still more pronounced when individual changes in maximal heart rate were considered (Fig. 4).

Table 3 *Changes after coronary bypass surgery in the patients with partial revascularisation*

	Incomplete revascularisation (n = 7)	*Partial graft failure (n = 16)*
Grafts: patent	8	10
occluded	—	10
$\dot{V}O_2$ 'max or SL'	+40%†	+11%
HR max	+28%†	+18%†
Postop angina	0/7	2/10
Postop MI	0/7	5/10
Ejection fraction	+3%	−14%
SV max*	—	−12%
CO max*	+34%	+11%
HR × BP max*	+31%	+34%†

*: 4 patients with incomplete revascularisation and 5 patients with partial graft failure.

†: P < 0·05; all other changes are not significant.

Discussion

The patients have been subdivided into 3 groups according to the degree of revascularisation which has been considered as adequate, partial, or none. This subdivision does not affect the data collected in the patients with adequate or no revascularisation; among the patients with adequate revascularisation, the presence in 10 patients of an ungrafted occluded artery did not influence the surgical results. As will be discussed below, the group with partial revascularisation is not homogeneous since patients with incomplete surgery appear to differ from those with partial graft failure. The subdivision into 3 groups is entirely based on postoperative data and the latter account for slight differences in the preoperative condition of the patients; those with adequate revascularisation had a slightly less severe

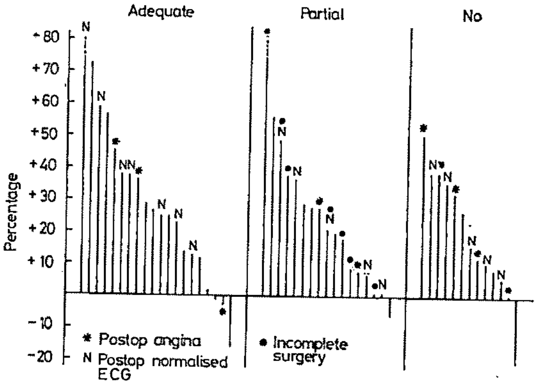

Fig. 4 *Individual changes in maximal heart rate after coronary bypass surgery.*

coronary heart disease and preoperative myocardial infarctions were more frequent in this group.

The graft patency rate noted in the present group of patients is very low (62%) and contrasts with the overall patency rate observed in our own institution (79%). The low patency rate reported here should, therefore, not be interpreted as resulting from poor surgical techniques since it is entirely the result of the mode of selection of the patients: many patients with good surgical results and patent grafts could not be included since they had no postoperative exercise studies.

Haemodynamic data were not collected in all 50 patients but the changes in physical working capacity, maximal heart rate, exertional angina pectoris, and resting ejection fraction measured in the 3 subsets of patients who underwent haemodynamic studies are practically identical to those observed in the 3 groups of patients: these haemodynamic data provide the information required to understand the mechanisms underlying the changes observed after coronary bypass surgery.

As previously observed, adequate revascularisation results in a spectacular improvement of the physical working capacity, with disappearance of exertional angina pectoris in most patients (Bartel *et al.*, 1973; Lapin *et al.*, 1973; Balcon *et al.*, 1974; Knoebel *et al.*, 1974; Siegel and Loop, 1976); the electrocardiographic abnormalities during exercise are significantly reduced but the electrocardiogram is rarely completely normal, suggesting some residual myocardial ischaemia. These effects are the result of the partial or complete relief of myocardial ischaemia which allows the patients to reach their predicted maximal heart rate without angina pectoris. The higher postoperative $\dot{V}_{O_2}$ max is the result of both an increased maximal cardiac output and an expanded (AV)O_2 difference during maximal exercise; the stroke volume and the mean pulmonary arterial pressure during maximal exercise are not significantly modified, nor are the ejection fraction and the LVEDP at rest. McDonough *et al.* (1974) reported a lower maximal stroke volume after coronary bypass surgery but they did not mention the status of the grafts. Our data suggest no major changes in the left ventricular function, which was not unexpected since before operation all patients had resting ejection fractions above 50 per cent; an improved left ventricular function at rest and during exercise has been observed in several patients after successful coronary bypass surgery, but, from the available published reports, there is no systematic trend toward significant and persistent improvement (Bourassa, 1973; Campeau *et al.*, 1974; Hamby *et al.*, 1974; Hammermeister *et al.*, 1974; Levine *et al.*, 1975; Ross, 1975; Barry *et al.*, 1976). Electrocardiographic signs of postoperative myocardial infarction were never observed after adequate revascularisation, which is possibly related to the high incidence of preoperative myocardial infarction in this group; the incidence of postoperative myocardial infarction is indeed less in those patients with preoperative myocardial infarction (Assad-Morell *et al.*, 1975).

In contrast, physical working capacity was unchanged after unsuccessful operation (Bartel *et al.*, 1973; Lapin *et al.*, 1973; Balcon *et al.*, 1974) despite a significant increase in maximal heart rate and the disappearance of exertional angina pectoris in 58 per cent of the patients; the electrocardiographic signs of myocardial ischaemia during maximal exercise were not significantly modified in these patients. The unchanged $\dot{V}_{O_2}$ max or $\dot{V}_{O_2}$SL observed after operation in these patients is related to an unchanged maximal cardiac output; the latter is entirely caused by a significant decrease in stroke volume during maximal exercise. This lower stroke volume during maximal exercise together with the significantly decreased ejection fraction at rest strongly suggest an impaired left ventricular function after unsuccessful surgery; interestingly, the LVEDP at rest was not modified in these patients after operation (Rutherford *et al.*, 1972).

A major factor responsible for these undesirable results appears to be the occurrence of perioperative myocardial infarction which was observed in 46 per cent (6/13) of the patients with no revascularisation and in 50 per cent (5/10) of the patients with partial revascularisation resulting from partial graft failure. Perioperative myocardial infarction was most often observed in the myocardial zone supplied by a grafted artery (9/11) and frequently associated with failure of the graft (8/11). These observations made on a limited number of patients suggest a close relation between graft failure and perioperative myocardial infarction but other studies, on larger populations, have clearly indicated that perioperative myocardial infarctions were frequently observed in the absence of graft failure (Assad-Morell *et al.*, 1975; Morton *et al.*, 1975; Sternberg *et al.*, 1975). The patients who had no electrocardiographic evidence of perioperative myocardial infarction had similar results; this is possibly because of the incidence of 'electrocardiographic silent' myocardial necrosis; both anatomical (Assad-Morell *et al.*, 1975) and isotope (Platt *et al.*, 1976) studies have indicated a high incidence of perioperative myocardial infarcts which were not detected by the routine 12 electrocardiograms lead. The incidence of total graft failure was clearly associated with a lower stroke volume during maximal exercise and a lower ejection fraction at rest (Bourassa *et al.*, 1972; Sternberg *et al.*, 1975; Barry *et al.*, 1976). These data indicate that though unsuccessful surgery often alleviates angina pectoris and does not reduce physical working capacity, the net result of total graft failure is often a significant impairment of the left ventricular function; the prognostic implications of this situation deserve further studies, but a worsened prognosis would not be surprising (Brewer *et al.*, 1972; Bruschke *et al.*, 1973; Schrank *et al.*, 1974).

The effects of partial revascularisation on the physical working capacity are intermediate (Knoebel *et al.*, 1974) and in our patients they appear to depend essentially on the presence or the absence of graft failure. When all grafts are patent but some significant lesions have not been bypassed, the results are close to those of adequate revascularisation, and perioperative myocardial infarctions have never been observed. On the other hand, the incidence of perioperative myocardial infarction is high in our patients with partial graft failure; the results are similar to those observed in the group with total graft failure, and similar signs of impaired left ventricular function are observed. These data are of practical importance since partial graft failure is not infrequent.

Several authors have reported that postoperative maximal exercise testing was a valuable method in the assessment of the results of coronary surgery (Bartel *et al.*, 1973; Guiney *et al.*, 1973; Lapin *et al.*, 1973; Balcon *et al.*, 1974; Merrill *et al.*, 1975); though the latter is true when groups of patients are considered, our data indicate that, in a given patient, it is often impossible to predict the degree of revascularisation from maximal exercise testing data because of the overlap between the groups. This is because of the frequent disappearance of angina pectoris after unsuccessful surgery and because of the increased maximal heart rate and maximal pressure-rate product observed in our patients with total graft failure; our findings which are similar to those recently reported by Siegel and Loop (1976) are in disagreement with previous studies indicating a good agreement between the changes in maximal heart rate or maximal pressure-rate product and graft patency (Lapin *et al.*, 1973; Merrill *et al.*, 1975). The reasons for these discrepancies are unclear.

We conclude from this study that in patients with normal preoperative ejection fraction, adequate revascularisation causes a significant improvement in physical working capacity; the left ventricular function does not appear to be modified and the observed improvement results from the prevention of angina pectoris which allows the patients to reach their predicted normal maximal heart rate. When all grafts are occluded, the physical working capacity is not significantly modified though the maximal heart rate is increased; the latter results from a lower stroke volume and ejection fraction which are likely to reflect an impaired left ventricular function and are often associated with perioperative myocardial infarction. The effect of partial revascularisation appears to be determined by the occurrence of partial graft failure. Individual changes in maximal exercise testing responses do not allow reliable predictions about the degree of surgical revascularisation.

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Plasma noradrenaline concentrations during isometric exercise

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SUMMARY Blood was collected simultaneously from the left ventricle and pulmonary artery in 12 patients undergoing routine cardiac catheterisation and was analysed for noradrenaline concentrations at rest, during, and after isometric stress (hand grip).

Moderate isometric exercise resulted in a significant rise in plasma noradrenaline with a return to basal values 10 minutes after discontinuing the grip test.

There were no significant differences in noradrenaline levels between the left ventricular and pulmonary arterial samples either at rest or during exercise.

Three patients with evident left ventricular dysfunction had the highest plasma noradrenaline concentrations, in contrast to the much lower levels in 2 patients on beta-blockers and in 1 patient with a normal heart.

As moderate isometric effort results in an important increase in noradrenaline level, this form of exercise could be dangerous in subjects suffering from ischaemic heart disease or in those with impaired left ventricular function since these patients are particularly susceptible to arrhythmias.

Isometric or static exercise exerts profound haemodynamic changes. An important arterial pressure rise is generated against a moderate rise only in heart rate and cardiac output, with little alteration in stroke volume (Lind and McNicol, 1967; Lind, 1970). This pressure response results from the combined effects of an increase in heart rate resulting from a release from vagal tone, a positive inotropic mechanism (Grossman *et al.*, 1973; Krayenbuehl *et al.*, 1973; Stefadouros *et al.*, 1974), and some peripheral vasoconstriction (Macdonald *et al.*, 1966; Freyschuss, 1970). It has been claimed that changes in plasma noradrenaline concentrations reflect the activity of the sympathetic nervous system (Lake *et al.*, 1976). The purpose of the current study was to investigate whether plasma noradrenaline levels were altered by isometric exercise and, if so, whether pulmonary arterial and left ventricular levels were different.

Subjects and method

Twelve consecutive patients (11 male, 1 female), with a mean age of 49·6 years (range 30-57 ± SD 7·3 years), had routine cardiac catheterisation. All patients gave their informed consent. All were fasting, in sinus rhythm, and premedicated with intramuscular diazepam 10 mg and promethazine hydrochloride 25 mg.

Resting heart rate and left ventricular systolic and diastolic pressures were recorded using Hewlett-Packard 120 series transducers and 350 series multichannel recording system at a paper speed of 25 mm/s. The zero reference point was taken at the mid chest position. The patient then performed a standardised hand-grip as described previously (Vecht, 1976). They were asked to squeeze a balloon dynamometer with their left hand to a level of 0·3 kg/cm^2 for a period of between 2 and 3 minutes while breathing normally. This degree of isometric effort can be comfortably performed by most patients and corresponds to a maximal voluntary capacity of approximately 30 per cent. The method has been fully described elsewhere (Krayenbuehl *et al.*, 1972). Recordings were again obtained at 1·5 and 3 minutes hand-grip and repeated 5 and 10 minutes after discontinuing the isometric effort. At equal time intervals, left ventricular and pulmonary arterial blood samples (10 ml) were collected simultaneously into lithium heparin tubes, centrifuged for 5 minutes, and the plasma immediately frozen at −20°C until assayed (within 21 days of collection).

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An average hand-grip of 0·29 kg/cm^2 ± SD 0·01 for a mean duration of 3 minutes 6 s ± SD 13 s was performed.

Patients on beta-antagonists were taken off these drugs 3 days before the study, except in 2 cases.

Cardiac indices at rest were derived from arteriovenous samples collected simultaneously; the oxygen uptake was estimated from tables (Robertson and Reid, 1952).

Ejection fractions at rest were calculated planimetrically from left ventricular angiograms using the area-length method (Kasser and Kennedy, 1969).

The plasma noradrenaline levels were estimated by a radio-enzymatic method (Henry *et al.*, 1975).

Results

Table 1 summarises the resting haemodynamic and angiographic data and the changes in plasma noradrenaline levels observed during maximal exercise.

ble 1 *Haemodynamic, angiographic, and plasma noradrenaline data*

e	*Age/Sex*	*Diagnosis*	*Cor. angio*	*LV Cine*	*Cardiac index (l/min per m^2)*	*Ejection fraction*		*Heart rate (bt/min)*	*LVSP (mmHg)*	*LV PNA (pg/ml)*	*PA PNA (pg/ml)*	*Hand-grip (kg/cm^2)*	*Beta-blocker*
	57/M	IHD	AD 1; C 1; RCA 1	Moderately good	2·9	0·67	R	71	161	405	—	0·3	None, chronic bronchitis
							HG$_2$	95	216	503	—	3 min	
							R$_{10}$	73(R$_5$)	184(R$_5$)	457(R$_5$)	—		
	48/M	IHD	AD 1	General hypokinesia	3·2	0·65	R	69	112	389	437	0·3	Metoprolol 50 mg b.d.
							HG$_2$	84	167	478	492	3 min 45s	
							R$_{10}$	81	116	383	410		
	51/F	IHD	AD-patchy atheroma	Normal	4·0	0·90	R	72	181	448	425	0·3	Propranolol 40 mg t.d.s.
							HG$_2$	81	214	560	607	3 min 15s	
							R$_{10}$			621	471		
	52/M	IHD	AD 2	Ant. wall hypokinesia	2·3	0·56	R	86	131	1025	997	0·27	None, asthma
							HG$_2$	101	156	1625	1708	3 min	
							R$_{10}$			1169(R$_5$)	1196(R$_5$)		
	57/M	IHD, BP ↑	Main stem LCA 2; RCA 2	Large apical LV aneurysm	3·6	0·37	R	76	168	434	465	0·3	Propranolol 160 mg q.d.s.
							HG$_2$	80	191	656	608	3 min	
							R$_{10}$			423	513		
	49/M	IHD	AD 3; C 2; RCA 1	Small ant. wall aneurysm; mild MR	3·5	0·86	R	63	106	327	331	0·28	Metoprolol 50 mg b.d.
							HG$_2$	93	183	504	737	3 min 15s	
							R$_{10}$			364	277		
	30/M	Normal	NAD	Normal	4·1	0·73	R	62	104	173	187	0·3	Metoprolol 100 mg b.d.
							HG$_2$	79	135	227	185	3 min	
							R$_{10}$			235	233		
	52/M	COCM	NAD	Gross hypokinesia	2·4	0·32	R	88	169	765	697	0·3	None, asthma
							HG$_2$	103	197	1121	997	3 min	
							R$_{10}$	86	167	943	341		
*	44/M	Mild BP ↑	NAD	LVH; moderate contraction	3·2	0·74	R	63	95	150	164	0·3	Propranolol 40 mg t.d.s.
							HG$_2$	83	133	259	232	3 min	
							R$_{10}$	64	103	205	137		
	55/M	IHD	AD 2; RCA 1; C 2	Good	3·7	0·86	R	67	151	314	383	0·3	Propranolol 20 mg t.d.s.
							HG$_2$	94	215	410	533	3 min	
							R$_{10}$	71	147	355	383		
	54/M	Severe MR	NAD	Large LV; moderate contraction	1·9	(X)	R	91	114	984	1189	0·3	None, heart failure
							HG$_2$	93	129	1066	943	3 min	
							R$_{10}$	88(R$_5$)	117(R$_5$)	902	1039		
**	47/M	IHD	AD 3; RCA 2	Good	3·0	0·71	R	84	133	120	140	0·3	Propranolol 10 mg t.d.s.
							HG$_2$	84	149	150	170	3 min	
							R$_{10}$			140	110		

reviations:

	Incalculable, severely reduced.	COCM	Congestive cardiomyopathy
	Diminished left ventricular function	MR	Mitral regurgitation
	On propranolol 120 mg/d	LVH	Left ventricular hypertrophy
	On propranolol 30 mg/d	n	Normal heart
	Blood pressure	IHD	Ischaemic heart disease
SP	Left ventricular systolic pressure	PNA	Plasma noradrenaline
	Left ventricle	R	Rest
	Pulmonary artery	HG$_2$	Maximal hand-grip
	Circumflex	R$_5$-R$_{10}$	5 and 10 minutes after stopping hand-grip
	Anterior descending	RCA	Right coronary artery

onary artery stenosis grading: 0, normal; 1, 50 to 75 per cent stenosis; 2, > 75 per cent stenosis; 3, total occlusion.
D, no abnormality detected.

Table 2 *Mean resting and hand-grip haemodynamics and plasma noradrenaline concentrations*

	Heart rate (bt/min)	*LVSP (mmHg)*	*LV PNA (pg/ml)*	*PA PNA (pg/ml)*
Rest	74	135	461	492
SE	3	8	88	102
Maximum hand-grip	89	174	630	655
SE	2	9	125	134
P	< 0·005	< 0·005	< 0·01	< 0·05
Difference	+ 15	+ 39	+ 169	+163

Abreviations:
PA, pulmonary artery; PNA, plasma noradrenaline;
LVSP, left ventricular systolic pressure; LV, left ventricle.

Table 2 compares the mean resting and maximal hand-grip heart rates, left ventricular systolic pressures, and left ventricular and pulmonary arterial noradrenaline concentrations.

During hand-grip there was a significant rise in mean heart rate (from 74 ± SE 3·0 beats/min at rest to 89 ± 2·4 beats/min at maximum hand-grip; $P < 0{\cdot}005$).

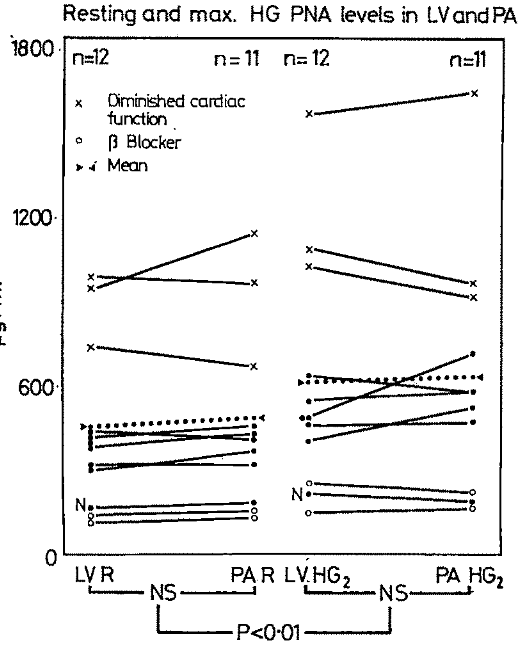

Fig. 2 *Resting left ventricular and pulmonary arterial plasma noradrenaline levels on left and during maximal hand-grip on right. Patient marked N considered to have normal heart.*

There was an equally significant rise in mean left ventricular systolic pressure (from 135 ± SE 8·5 mmHg at rest to 174 ± 9·6 mmHg at maximum hand-grip; $P < 0{\cdot}005$) (Fig. 1). The mean resting left ventricular plasma noradrenaline level was 461·0 ± SE 88·3 pg/ml, rising significantly to 630·0 ± 125·0 pg/ml at maximum hand-grip; $P < 0{\cdot}01$. This represented a 36·6 per cent rise. The mean resting pulmonary arterial plasma noradrenaline was 492·0 ± SE 102·4 pg/ml, which rose significantly to 655·0 ± 134·7 pg/ml at maximum hand-grip ($P < 0{\cdot}05$), a percentage rise of 33·1 (Fig. 2).

Neither resting nor hand-grip pulmonary arterial noradrenaline was significantly different from left

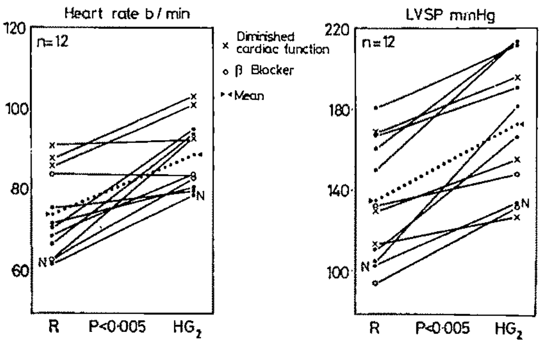

Fig. 1 *Resting (R) and maximal hand-grip (HG_2) heart rates on the left; left ventricular systolic pressures on the right. Patient marked N considered to have normal heart.*

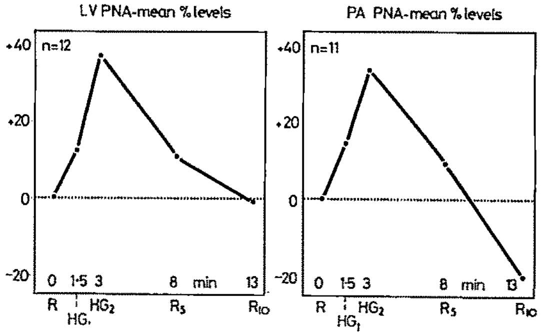

Fig. 3 *Mean plasma noradrenaline percentage changes in left ventricle on left and pulmonary artery on right. HG_1 represents samples taken at 1·5 minutes of hand-grip; HG_2 equals maximal hand-grip at 3 minutes. R_5 and R_{10}: samples at 5 and 10 minutes after discontinuing hand-grip.*

ventricular concentrations. These levels returned to basal values 10 minutes after stopping the isometric exercise. Fig. 3 shows the mean percentage rise in plasma noradrenaline left ventricular and pulmonary arterial samples.

Three patients in this series had cardiac indices below 2·5 l/min per m^2 and poor ejection fractions with severe radiological abnormalities of left ventricular wall motion. These patients had the highest resting and exercise noradrenaline levels.

The 2 patients studied while still on beta-blockers and the one patient considered to have a normal heart had the lowest resting and exercise noradrenaline levels (Fig. 2).

Discussion

Emotional stress (Passon and Peuler, 1973), noise (Aronow *et al.*, 1973), posture (Lake *et al.*, 1976), and dynamic and isometric exercise (Kozlowksi *et al.*, 1973; Lake *et al.*, 1976) are known to stimulate the release of noradrenaline from sympathetic postganglionic nerve terminals.

In healthy subjects, isometric effort was associated with a greater rise in venous noradrenaline than that observed during dynamic work involving large muscle groups (Kozlowski *et al.*, 1973).

In the present study, 12 patients with various cardiac pathologies requiring invasive investigations were found to have a significant rise in plasma noradrenaline in response to a limited moderate grip test. The increase in plasma noradrenaline was of the same magnitude and not significantly different when comparing samples obtained from within the left ventricular cavity or from the pulmonary arterial lumen. This suggested that the pressor response resulting from isometric stressing was accompanied by an overall increase in sympathetic tone rather than an isolated discharge from cardiac nerve endings.

Others have shown in a group of postoperative patients that venous noradrenaline levels were significantly higher than arterial samples (Lake *et al.*, 1976) and this has been attributed to the removal of noradrenaline during lung passage (Gillis *et al.*, 1972). This was not the case in the current study since left ventricular and pulmonary arterial noradrenaline concentrations were not significantly different when compared at rest or during hand-grip.

It has been suggested that the pressor response induced by isometric effort is a reflex (initiated by an accumulation of metabolites within the muscles) designed to maintain adequately perfused contracting muscles (Coote *et al.*, 1971).

We have shown an appreciable rise in plasma noradrenaline at 1·5 minutes of sustained muscular contraction, whereas others have shown a significant rise within 30 seconds only (Kozlowski *et al.*, 1973).

The dimension of the pressor response is not related to the mass of the contracting musculature but to the tension developed by a single group of muscles, however small (Lind, 1970). So forceful is this vasopressor reflex that it is not abolished by beta-receptor antagonists (Macdonald *et al.*, 1966; Shaver *et al.*, 1972; Vecht *et al.*, 1972), the rise in pressure in this situation being dependent on an increase in peripheral resistance (Tarazi and Dustan, 1971).

Two patients in this series who were on beta-adrenergic blocking agents at the time of cardiac catheterisation had very low resting as well as hand-grip noradrenaline levels. It appears that beta-adrenergic antagonists may reduce circulating catecholamines in patients with cardiac disorders and in some way attenuate the vasopressor response to isometric stress (Vecht *et al.*, 1972). The underlying mechanism, however, remains obscure. A central effect or alternatively a peripheral antagonism of presynaptic beta-receptors could explain these observations. It is noteworthy that Naylor reported diminished release of noradrenaline from the coronary sinus after beta-blockade when dog hearts were stimulated electrically (Nayler and Chang, 1973). One man in this series, with a normal heart, also had low noradrenaline levels compared with the other patients investigated. At the other extreme, 3 patients with impaired left ventricular performance were found to have very high circulating noradrenaline levels which rose further during isometric stressing. These patients presumably required an increased sympathetic drive to maintain an adequate cardiac output.

Isometric exercise is also known to induce ventricular ectopy (Matthews *et al.*, 1971). In patients with complete atrioventricular block, small doses of noradrenaline (as opposed to adrenaline infusions) were associated with ventricular extrasystoles (Zoll *et al.*, 1955). It seems likely that the ventricular arrhythmias frequently encountered during hand-gripping are related to the concentration of circulating noradrenaline.

It, therefore, appears justifiable to plead for caution when subjecting patients suffering from ischaemic heart disease or left ventricular dysfunction to isometric exercise and perhaps even proscribe its use from cardiac rehabilitating centres.

We thank Dr E. M. M. Besterman for permission to study his patients.

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Addendum

Six additional patients have been studied in a similar way. One of these patients was in heart failure and very high resting and hand-grip plasma noradrenaline levels were found.

In all 6 patients left ventricular and pulmonary arterial noradrenaline levels were again of similar magnitude both at rest and during hand-grip.

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Coronary and myocardial metabolic effects of combined glyceryl trinitrate and propranolol administration

Observations in patients with and without coronary disease

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SUMMARY Coronary haemodynamic and metabolic effects of propranolol and glyceryl trinitrate were studied in 12 patients with coronary artery disease and 5 without coronary heart disease, at rest and during tachycardia stress. Propranolol-associated reductions in indices of myocardial oxygen demand, left ventricle work, tension time, and left ventricle oxygen utilisation ($LV\dot{V}O_2$) were reversed when heart rate was controlled by atrial pacing. Adding glyceryl trinitrate at rest also restored heart rate but decreased the left ventricular work index and tension time index as coronary resistance declined paradoxically. Tachycardia-related increases in tension time index and $LV\dot{V}O_2$ were unchanged after propranolol, and ischaemia (angina, ST depression, and reduced lactate extraction) was not altered in most of the patients. During tachycardia, the addition of glyceryl trinitrate decreased the tension time index and $LV\dot{V}O_2$; angina recurred in only 4 patients, and ST depression and lactate extraction improved. Similar haemodynamic changes occurred in the patients with normal coronary arteries.

In contrast with propranolol administered alone, propranolol plus glyceryl trinitrate enhances tachycardia tolerance and prevents tachycardia-induced manifestations of ischaemia. This action is attributed to glyceryl trinitrate-associated improvement in the adequacy of myocardial perfusion.

Although nitrates are frequently used in combination with propranolol and have been justified by clinical and haemodynamic rationale (Russek, 1968; Wiener *et al.*, 1969; Aronow, 1972), there is no information on the effect of this combination on the coronary circulation. Propranolol is known to reduce stress-related augmentation of cardiac rate, contractility, and work—all of which have prominent oxygen-sparing effects (Dwyer *et al.*, 1968; Wiener *et al.*, 1969). Some have suggested that this agent also directly affects the coronary circulation and reduces myocardial flow (Parratt, 1965; Wolfson *et al.*, 1966; Nayler *et al.*, 1967, 1968; Stein *et al.*, 1968; Marchetti *et al.*, 1972) and oxygen consumption (Jorgensen *et al.*, 1973; Mueller *et al.*, 1974) while increasing coronary resistance. Since the effect of propranolol on heart rate also uniformly decreases oxygen requirements, significant direct coronary actions may be obscured. Glyceryl trinitrate, on the other hand, also has oxygen-sparing effects that reduce ventricular pressure (Bernstein *et al.*, 1966), size (William *et al.*, 1965), and work (Robin *et al.*, 1967) determinants of oxygen demand. Though there is angiographic evidence that sublingual glyceryl trinitrate produces coronary dilatation (Likoff *et al.*, 1964), most studies generally have indicated that coronary flow is unchanged or declined in patients with coronary disease (Gorlin *et al.*, 1959; Parker *et al.*, 1971). This presumably is in response to reduced oxygen demand.

Because information describing the effects of glyceryl trinitrate on coronary haemodynamics and metabolism in the presence of beta-blockade was not available, we studied (1) the coronary haemo-

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dynamic, metabolic, and antianginal actions of glyceryl trinitrate in patients with angina pectoris after pretreatment with propranolol; (2) the therapeutic efficacy of glyceryl trinitrate in the beta-blocked patient on tachycardia-induced ischaemia; and (3) the importance of chronotropic influences of these agents on these responses. To circumvent propranolol's chronotropic effects, we used atrial pacing to control heart rate and also to evoke angina. Alterations in chest pain and coronary flow, as reflected in the coronary sinus blood flow, and systemic haemodynamic and myocardial metabolic responses occurring during tachycardia were compared before and after administering propranolol and glyceryl trinitrate.

Patients and methods

Twelve patients with clinically stable angina pectoris (New York Heart Association Class II or III) associated with ≧ 75 per cent coronary artery diameter narrowing were studied. Informed consent was obtained to include the procedures outlined subsequently. All antianginal agents were omitted for at least 1 week before study, but use of glyceryl trinitrate was permitted until the study day. Five patients with normal coronary and left ventricular angiography were also studied. None had anatomical or physiological evidence of other forms of heart disease.

With the patients in a postabsorptive state and without premedication, a No. 18 Teflon catheter was inserted percutaneously into a brachial artery, and systemic pressure was measured (Statham P23Db transducer). Mean arterial pressure was obtained by electric filtering. A specially designed No. 7 pacing catheter (Wilton Webster Co.) was positioned in the midcoronary sinus from a median cubital vein. This catheter was modified to measure coronary sinus blood flow by the continuous thermodilution method (Ganz *et al.*, 1971). The procedures used in our laboratory to determine coronary sinus blood flow, verify catheter position, and simultaneously measure cardiac output and prevent blood volume changes are described elsewhere (Pepine *et al.*, 1974). Electrocardiographic lead V5 was monitored continuously; and the standard limb leads were recorded before, during, and after pacing-induced angina. The ST segment change from control was measured in the 3 to 5 beats after termination of pacing stress to avoid pacing-induced artefacts. Horizontal or down-sloping ST changes of 0·8 s or greater in duration, persisting in 3 consecutive beats, were reported. Recording speed was usually 25 mm per second, but 200 mm per second was used to measure systolic ejection and diastolic filling periods. During determinations of cardiac output and coronary sinus blood flow, 10 mm per second was used. Diastolic pressure time index was calculated according to Barnard and co-workers (1973) and the ratio of the diastolic pressure time index to tension time index was determined (Buckberg *et al.*, 1972). Simultaneously obtained coronary sinus and arterial blood samples were analysed in duplicate for oxygen and lactate contents by methods previously described (Pepine *et al.*, 1974).

Table 1 *Outline of study periods*

I. Control measurements
    Rest
    Tachycardia

II. Propranolol, 10 mg IV
    Propranolol
    Propranolol—heart rate at control rest level
    Propranolol—tachycardia

III. Glyceryl trinitrate, 0·3 mg SL
    Propranolol + glyceryl trinitrate
    Propranolol + glyceryl trinitrate—heart rate at control rest level
    Propranolol + glyceryl trinitrate—tachycardia

The experimental design is illustrated in Table 1. After catheters were in position and heart rate and mean arterial pressure stabilised, control resting measurements were made of mean arterial pressure, cardiac output, heart rate, coronary sinus blood flow, and myocardial oxygen and myocardial lactate extractions. Heart rate was then increased by increments of 10 beats per minute until angina occurred, and measurements were repeated before pacing was terminated. After symptoms subsided and ST segment and haemodynamic changes returned to resting levels, propranolol (10 mg) was administered intravenously (1 mg/min). Ten minutes later, measurements were repeated. The heart rate was then controlled by atrial pacing at the same resting heart rate that had been observed before propranolol, and measurements were repeated. Measurements were made as a repeat tachycardia stress test was performed. During this repeat test, heart rate and the duration of increment change duplicated the predrug test. After symptoms subsided and ST segment and haemodynamic changes returned to resting levels, glyceryl trinitrate (0·3 mg sublingually) was given. Measurements were repeated 2 to 3 minutes after the glyceryl trinitrate dissolved and heart rate and mean arterial pressure changes stabilised. When necessary, resting heart rate was again controlled by pacing to resting levels before propranolol administration. Heart rate was then increased as in the previous stress tests to the rate at which angina occurred in the control period. Measurements were repeated with tachycardia stress

Table 2 *Summary of clinical findings in the patients with coronary artery disease*

Case	*Sex*	*Age*	*MI*	*Coronary angiography**					*Tachycardia stress*								
									Angina			*ST depression (mm)*			*Abnormal lactate extraction†*		
				RCA	*MLCA*	*LAD*	*LCX*	*Coll*	*T*	*Tp*	*Tpn*	*T*	*Tp*	*Tpn*	*T*	*Tp*	*Tpn*
1	M	61	0	0	0	99	75	+	+	+	0	1·2	1·0	0·5	+	+	0
2	F	59	0	100	0	0	75	0	+	+	0	1·0	1·0	0·0	0	+	0
3	M	35	+	100	0	50	50	+	+	+	0	1·0	1·2	0·3	0	0	0
4	F	55	0	75	0	75	75	+	+	+	0	0·7	0·9	0·0	+	+	0
5	M	52	+	0	0	25	100	0	+	+	+	0·0	0·0	0·0	+	+	0
6	M	49	0	50	50	100	100	0	+	+	0	1·3	1·0	0·5	0	0	0
7	M	53	0	0	0	95	100	0	+	+	+	1·0	0·8	1·0	+	+	+
8	M	55	+	75	0	0	95	0	+	0	0	1·2	1·2	0·7	0	0	0
9	M	55	0	100	0	75	75	+	+	+	+	1·1	1·0	0·5	0	+	0
10	M	44	+	100	0	25	0	+	+	+	0	0·0	0·0	0·0	+	0	0
11	M	46	0	25	0	90	90	+	+	+	+	1·1	1·0	0·8	0	0	+
12	M	50	+	95	10	90	95	+	+	0	0	1·0	1·2	0·3	+	+	0

MI, myocardial infarction; RCA, right coronary artery; MLCA, main left coronary artery; LAD, left anterior descending; LCX, left circumflex coronary arteries, respectively; Coll, coronary collaterals; T, Tp, Tpn refer to tachycardia stress test in control, propranolol, and propranolol + nitroglycerine periods, respectively; 0, No; +, Yes.

*Per cent diameter reduction from 0-100.

†Lactate extraction < 10 per cent.

and glyceryl trinitrate and pacing terminated. In the 5 patients with normal coronary arteries, tachycardia measurements were made at 85 per cent of their maximal predicted heart rate (3 patients) or at peak heart rate achieved before limited by AV block (2 patients).

The following calculations were made: CI = CO/body surface area in m^2 (litres/m^2); MSER = CI/HR per SEP (ml/s per m^2); TTI = SPm × SEP × HR (mmHg s/min); LVWI = SPm × CI × 1·36/100 (kg m/min per m^2); CRI = SPm/CSBF (resistance units); $LV\dot{V}O_2$ = CSBF × arterial-coronary sinus oxygen content ÷ arterial lactate × 100 (%). The ratio of LVWI/$LV\dot{V}O_2$ was used as an index of left ventricular mechanical efficiency. Means and standard errors of the mean were calculated and compared by the t test for paired data.

Results

CLINICAL RESPONSES

Pertinent clinical data are summarised in Table 2. Typical angina, occurring during control tachycardia at a mean heart rate of 120 beats per minute in each of the 12 patients with coronary artery disease, recurred after pacing in 10 at the same heart rate. ST depression was not significantly altered. After the administration of glyceryl trinitrate, 6 additional patients did not experience angina. Significant change occurred in average ST segment depression produced by the same tachycardia stress after administration of glyceryl trinitrate (0·88 ± 0·13 to 0·38 ± 0·1 mm, $P < 0·05$). ST depression was less in 7 of the 8 who did not experience pacing-induced angina. The absence of pacing-induced angina could not be predicted by any other clinical or haemodynamic feature analysed.

SYSTEMIC AND CORONARY HAEMODYNAMIC MEASUREMENTS

Propranolol reduced resting heart rate (73 ± 2 to 67 ± 2 beats/min, mean ± SEM, $P < 0·01$.) This effected proportional reduction of the tension time index (8·5%) and cardiac index (10%) with related decrements in $LV\dot{V}O_2$ (7·6%) and coronary sinus blood flow (11%) as the coronary resistance index increased (12%), all $P < 0·05$. When heart rate was returned to control levels, no significant changes were observed (Table 3). The addition of glyceryl trinitrate restored heart rate (67 to 70 ± 3 beats/min), but significant reduction in cardiac, tension time, left ventricular work, and diastolic pressure time indices and ejection rate persisted, though the coronary resistance index was decreased as compared with propranolol resting values. In some patients, heart rate remained several beats slower than resting control rate after glyceryl trinitrate was added. Returning heart rate to control values (atrial pacing) did not influence the reduction noted above (Table 3).

With tachycardia stress, propranolol reduced the cardiac and left ventricular work indices and mean systolic ejection rate. Coronary sinus blood flow and coronary resistance index were not appreciably altered, as compared with control tachycardia. In

Table 3 *Summary of systemic and coronary haemodynamic effects at the same heart rate in patients with coronary artery disease (N = 12)*

	Rest (heart rate = 72 ± 2 beats/min)			*Tachycardia (heart rate 120 ± 5 beats/min)*		
	Control	*Propranolol*	*Propranolol + glyceryl trinitrate*	*Control*	*Propranolol*	*Propranolol + glyceryl trinitrate*
CI (l/min per m²)	3·4 ± 0·2	3·3 ± 0·2	2·9 ± 0·3	3·8 ± 0·2	3·3 ± 0·3	3·1 ± 0·3
TTI (mmHg s/min)	2002 ± 135	2110 ± 144	1815 ± 112	2887 ± 201	3048 ± 250	2714 ± 205
LVWI (kg m/min per m²)	4·3 ± 0·2	4·4 ± 0·3	3·4 ± 0·3	5·2 ± 0·4	4·7 ± 0·3	4·0 ± 0·4
MSER (ml/s per m²)	155 ± 8	152 ± 10	135 ± 10	133 ± 6	117 ± 8	115 ± 10
DPTI (mmHg s/min)	3146 ± 171	3456 ± 188	2952 ± 156	2852 ± 192	3002 ± 200	2837 ± 180
DPTI/TTI	1·57 ± 0·1	1·64 ± 0·07	1·62 ± 0·1	1·03 ± 0·09	0·99 ± 0·08	1·06 ± 0·1
CSBF (ml/min)	123 ± 10	129 ± 12	122 ± 10	164 ± 13	160 ± 15	137 ± 11
CR (mmHg/ml per min)	0·8 ± 0·07	0·91 ± 0·1	0·7 ± 0·05	0·67 ± 0·09	0·7 ± 0·09	0·7 ± 0·08

Abbreviations: CI, cardiac index; CR, coronary resistance index; CSBF, coronary sinus blood flow; DPTI, diastolic pressure time index; LVWI, left ventricular work index; MSER, mean systolic ejection rate; TTI, tension time index.
*P < 0·01, †P < 0·05—the only significant comparisons.

contrast, the addition of glyceryl trinitrate reduced the tension time, diastolic pressure time, and left ventricular work indices and coronary sinus flow during tachycardia stress, compared with values after propranolol (Table 3). When compared with control, tachycardia, cardiac index, left ventricular work index, mean systolic ejection rate, and coronary sinus blood flow declined.

INDICES OF MYOCARDIAL METABOLISM AND EFFICIENCY

Analysis of the effects of propranolol on myocardial metabolism revealed that $LV\dot{V}O_2$ declined (12%, $P < 0·05$), whereas lactate extraction and $LVWI/LV\dot{V}O_2$ were not significantly influenced. When heart rate was controlled, $LV\dot{V}O_2$, lactate extraction, and $LVWI/LV\dot{V}O_2$ were not significantly different from control values (Table 4). The addition of glyceryl trinitrate, however, lowered the left ventricular work index disproportionately, so that $LVWI/LV\dot{V}O_2$ decreased significantly (25%, $P < 0·01$) from levels after propranolol alone. Though lactate extraction decreased, the values were not significant ($P = 0·05$).

With tachycardia stress, propranolol decreased $LVWI/LV\dot{V}O_2$ (0·36 to 0·28, $P < 0·01$), compared with values observed after propranolol administration with the subject at rest, through a disproportionate decline in left ventricular work index. The decline in lactate extraction became significant after propranolol (29 to 9%, $P < 0·05$). After glyceryl trinitrate was added, $LV\dot{V}O_2$ declined as compared with propranolol values (17·9 to 15·0). Abnormal decrements in $LVWI/LV\dot{V}O_2$ and lactate extraction did not occur. Lactate extraction was reversed 9·0 to 27%.

Data from the patients with normal coronary arteries are summarised in a similar manner in Tables 5 and 6. Propranolol also reduced the resting heart rate (72 ± 4 to 67 ± 3 beats/min) in these patients as coronary sinus blood flow (8·3%), tension time index (10%), and cardiac index (8%) declined and coronary resistance increased (11%). Again at the same heart rate and after glyceryl trinitrate, no significant systemic or coronary haemodynamic differences occurred (Tables 3 and 5). As expected, because more tachycardia stress was tolerated by these normal patients (137 *vs.* 120

Table 4 *Summary of metabolic effects of glyceryl trinitrate after propranolol at same heart rate in patients with coronary artery disease (N = 12)*

	Rest (heart rate = 72 ± 2 beats/min)			*Tachycardia (heart rate = 120 ± 5 beats/min)*		
	Control	*Propranolol*	*Propranolol + glyceryl trinitrate*	*Control*	*Propranolol*	*Propranolol + glyceryl trinitrate*
LV O_2 utilisation (ml/min)	13·5 ± 0·97	12·8 ± 1·3	12·9 ± 1·0	18·5 ± 1·6	17·9 ± 1·9	15·0 ± 1·3
LV O_2 extraction (%)	65 ± 2	64 ± 2	63 ± 2	65 ± 1·2	63 ± 2	64 ± 2
Lactate extraction (%)	27 ± 8	29 ± 9	17 ± 4	18 ± 5	9 ± 5	27 ± 1
LVWI/LV$\dot{V}O_2$	0·33 ± 0·02	0·36 ± 0·03	0·27 ± 0·03	0·30 ± 0·03	0·28 ± 0·03	0·27 ± 0·02

Abbreviations: LV, left ventricle; LV O_2, left ventricle oxygen; LVWI, left ventricle work index; LV$\dot{V}O_2$, left ventricle oxygen utilisation index; LVWI/LV$\dot{V}O_2$, mechanical efficiency index; *P < 0·01—the only significant comparison.

beats/min), coronary sinus blood flow and related values were considerably higher. Except for an increase in lactate extraction with tachycardia before (16 to 22, P = 0·1) and after (20 to 29, P < 0·05) propranolol, no differences in metabolism or efficiency indices resulted (Tables 4 and 6).

Table 5 *Summary of systemic and coronary haemodynamic effects at same heart rate in patients with normal coronary arteries (N = 5)*

	Rest (heart rate = 72 ± 4 beats/min)			*Tachycardia (heart rate = 137 ± 6 beats/min)*		
	Control	*Propranolol*	*Propranolol + glyceryl trinitrate*	*Control*	*Propranolol*	*Propranolol + glyceryl trinitrate*
CI (litres/min per m^2)	3·7 ± 0·4	3·0 ± 0·2	2·6 ± 0·2	4·2 ± 0·4	3·4 ± 0·3	2·8 ± 0·2
TTI (mmHg s/min)	2150 ± 143	2140 ± 156	1789 ± 131	3229 ± 199	3235 ± 164	2700 ± 94
LVWI (kg m/min per m^2)	5·0 ± 0·6	4·1 ± 0·4	3·1 ± 0·3	5·7 ± 0·6	4·8 ± 0·5	3·4 ± 0·3
MSER (ml/s per m^2)	168 ± 10	140 ± 9	121 ± 10	139 ± 8	115 ± 9	112 ± 9
DPTI (mmHg s/min)	3182 ± 201	3210 ± 213	2505 ± 187	2519 ± 160	2588 ± 192	2214 ± 158
DPTI/TTI	1·48 ± 0·1	1·5 ± 0·1	1·4 ± 0·1	0·78 ± 0·09	0·80 ± 0·08	0·82 ± 0·1
CSBF (ml/min)	99 ± 7	102 ± 6	76 ± 6	143 ± 15	151 ± 17	104 ± 8
CR (mmHg/ml per min)	1·0 ± 0·05	0·99 ± 0·08	1·2 ± 0·07	0·73 ± 0·07	0·72 ± 0·07	0·80 ± 0·07

Abbreviations: CI, cardiac index; TTI, tension time index; LVWI, ventricular work index; MSER, mean systolic ejection rate; DPTI, diastolic pressure time index; CSBF, coronary sinus blood flow; CR, coronary resistance index.
*P < 0·01, †P < 0·05—the only significant comparisons.

Table 6 *Summary of metabolic effects at same heart rate in patients with normal coronary arteries (N = 5)*

	Rest (heart rate = 72 ± 4 beats/min)			*Tachycardia (heart rate = 137 ± 6 beats/min)*		
	Control	*Propranolol*	*Propranolol + glyceryl trinitrate*	*Control*	*Propranolol*	*Propranolol + glyceryl trinitrate*
$\text{LV}\dot{\text{V}}\text{O}_2$ (ml/min)	10·8 ± 1·1	11·0 ± 1·3	8·6 ± 1·2	16·4 ± 2·7	15·5 ± 2·5	10·9 ± 1·5
LV O_2 extraction (%)	67 ± 4	68 ± 4·1	70 ± 4·2	71 ± 4·3	70 ± 4·2	72 ± 4·5
Lactate extraction (%)	16 ± 7	20 ± 8	27 ± 12	22 ± 7	29 ± 11	30 ± 12
$\text{LVWI}/\text{LV}\dot{\text{V}}\text{O}_2$	0·44 ± 0·08	0·41 ± 0·1	0·38 ± 0·09	0·45 ± 0·11	0·36 ± 0·08	0·35 ± 0·06

Abbreviations: $\text{LV}\dot{\text{V}}\text{O}_2$, left ventricular oxygen utilisation; $\text{LVWI}/\text{LV}\dot{\text{V}}\text{O}_2$, mechanical efficiency index.
*P < 0·01, †P < 0·05—the only significant comparisons.

Discussion

Glyceryl trinitrate is widely used in combination with propranolol for the treatment of angina pectoris. The therapeutic benefit of this drug combination results from a complex interaction of multiple cardiovascular responses (Goldstein and Epstein, 1972). Propranolol-related actions contributing to this response include negative chronotropic and inotropic effects (Dwyer *et al.*, 1968; Wiener *et al.*, 1969). Counteracting these salutary responses, there is evidence implying that this agent may also increase ventricular size and the duration of systole (Goldstein and Epstein, 1972). The latter effects would tend to augment oxygen consumption by increasing wall tension. Additionally, the possibility of a coronary vasoconstricting action has been suggested (Marchetti *et al.*, 1972). Glyceryl trinitrate, on the other hand, reduces coronary perfusion pressure but may increase coronary flow at least transiently in some patients (Goldstein and Epstein, 1972). However, its major beneficial effect is thought to relate to reduced ventricular size and pressure. These actions decrease tension and shorten the duration of systole, thereby reducing oxygen consumption. Glyceryl trinitrate baroreceptor-mediated effects, however, increase heart rate and contractility. In the light of the foregoing, others have postulated that the negative chronotropic and inotropic actions of propranolol tend to offset potentially deleterious reflex effects of glyceryl trinitrate (Wiener *et al.*, 1969; Goldstein and Epstein, 1972), and its ability to decrease ventricular size and the duration of systole counterbalances the possible disadvantageous actions of propranolol. Thus, though the net contributions of these responses alone and the role of direct coronary actions have not yet been completely defined, this drug combination appears to be clinically beneficial.

The present study indicates that the antianginal action of propranolol, shown in previous investigations using exercise-evoked angina, is not prominent when heart rate is controlled. Supporting this subjective response was the absence of significant electrocardiographic, haemodynamic, or metabolic data to suggest improvement in the oxygen demand-supply relation. Some evidence also suggested that depression of haemodynamic function persists at the same heart rate. No findings to support a direct coronary action of propranolol were observed when the heart rate was controlled. The addition of glyceryl trinitrate after propranolol favourably influenced the tachycardia/angina threshold and demonstrated that heart rate changes are not of major importance in the anti-ischaemic action of this drug combination. The latter apparently derives from reduced oxygen consumption at a given level of tachycardia stress. Though this response results in reduced tachycardia coronary flow, the flow level appears adequate for the reduced oxygen demands because the clinical, electrocardiographic, and metabolic ischaemic indices improved.

This depression of left ventricular oxygen utilisation by the addition of glyceryl trinitrate, independent of heart rate, suggests that reduction of tension was of primary importance. Evidence for a coronary circulatory effect is suggested by the reduced coronary resistance index observed after glyceryl trinitrate was added. Because heart rate was controlled and other factors relating to oxygen requirements declined with the addition of glyceryl trinitrate, the decline in coronary resistance cannot be attributed to increases in myocardial oxygen demand. It is possible for an agent to reduce coronary resistance by augmenting oxygen consumption and not be reflected in these indices through increases in cardiac size or contractility. The former is at variance to the known action of glyceryl trinitrate on ventricular size. The latter is unlikely, since changes in contractility caused by reflex or general release of catecholamines should have been blocked by the propranolol. Furthermore, because a decline in tension and work indices would be expected to cause coronary vasoconstriction, the observed reduction in resistance may underestimate the degree of vasodilatation influence.

The magnitude of the coronary resistance decline at rest after administration of glyceryl trinitrate was quantitatively similar to that observed during tachycardia-induced angina before treatment. When $LV\dot{V}O_2$ was again increased in response to the demands imposed by tachycardia stress after glyceryl trinitrate, no further decline in coronary resistance accompanied this usually potent stimulus to vasodilatation. These findings suggest that either maximum dilatation of the diseased coronary bed had already occurred or that reduction of diastolic pressure time by glyceryl trinitrate abbreviated potential flow responses to augmented oxygen demands. Possibly a combination of these effects occurred. This could explain the finding that several patients still experienced angina after this usually potent combination, and it warrants more detailed investigation.

Several limitations to the coronary sinus sampling techniques have been reviewed elsewhere but should be re-emphasised (Klocke, 1975). In a segmental disease, such as coronary artery disease, regional alteration in perfusion and metabolism may not necessarily be reflected in the total coronary sinus effluent. Findings of a relatively high coronary sinus oxygen concentration in some patients with coronary artery disease support this assumption and suggest that midcoronary sinus sampling may actually be weighed in favour of relatively normally perfused areas of myocardium. Because of this limitation, we felt that considerable additional insight into the mechanism responsible for the coronary actions observed could be obtained by extending these observations to patients with normal coronary arteries. Interestingly, with the exception of the lactate changes, these normal subjects responded similarly to propranolol. After administration of glyceryl trinitrate, however, pronounced tachycardia-induced changes in coronary blood flow and resistance persisted. Though not conclusive, this finding supports the suggestion that the maximum dilatory capacity of the patient with coronary disease is very limited.

These findings are of clinical interest in treating patients with coronary heart disease. For example, patients with acute myocardial ischaemia who develop tachyarrhythmias that persist after propranolol therapy may be at a distinct disadvantage. The evidence presented indicates that adding glyceryl trinitrate under these circumstances is particularly advantageous. Its use should not be delayed pending the evaluation of other therapeutic interventions.

In conclusion, glyceryl trinitrate appears to retain its potentially beneficial coronary haemodynamic and metabolic actions in the presence of beta-blockade. The oxygen cost of a given tachycardia stress is reduced, and evidence for resting coronary vasodilatation is present. Because deterioration of myocardial lactate metabolism and efficiency during tachycardia is prevented, the adequacy of myocardial perfusion is improved. These data indicate that an important advantage relative to the coronary circulation ensues when glyceryl trinitrate is used in the presence of propranolol.

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Influence of glyceryl trinitrate during supine and upright exercise in patients with angina pectoris[1]

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SUMMARY The clinical, electrocardiographic, and circulatory effects of 0·6 mg sublingual glyceryl trinitrate were studied at rest and during treadmill and supine bicycle exercise in 16 patients with angina pectoris. Before glyceryl trinitrate, all patients experienced angina during both exercise periods. However, the heart rate and rate pressure product at angina were higher during treadmill than during supine bicycle exercise. This is considered to be the result of diminished left ventricular volume and oxygen requirements in the upright posture.

At rest after glyceryl trinitrate, systolic blood pressure fell and heart rate rose in each posture, the effects being more pronounced in the standing position. During exercise, when the rate pressure product at the onset of angina before glyceryl trinitrate was compared with the rate pressure product at the same work load after glyceryl trinitrate, there was no significant difference in either position (treadmill, 192 ± 10 vs 203 ± 9; supine, 185 ± 9 vs 182 ± 8 mmHg/min × 10^{-2}). However, in comparison with the control values before glyceryl trinitrate, exercise duration to angina after glyceryl trinitrate increased significantly in each posture. The rate pressure product at angina after glyceryl trinitrate increased significantly in comparison with the rate pressure product at angina during the control studies in each posture. The improvement in exercise tolerance and increase in rate pressure product after glyceryl trinitrate were similar during both upright and supine exercise. This could be interpreted as evidence for the predominant influence of glyceryl trinitrate on coronay perfusion but it is possible that similar changes in ventricular volume during exercise occurred in both positions.

Patients with angina pectoris have better exercise tolerance and achieve higher rate pressure products in the upright than in the supine posture (Lecerof, 1971; Bygdeman and Wahren, 1974). This probably reflects reduced left ventricular volume with resultant decrease in wall tension and myocardial oxygen requirements for any given rate pressure product in the upright posture. This is supported by the observation that left ventricular filling pressures during exertional angina are lower during upright than during supine exercise (Thadani *et al.*, 1977). Glyceryl trinitrate, by its venous and arteriolar effects (Mason and Braunwald, 1965), reduces left ventricular volume (Burggraf and Parker, 1974) which should be more pronounced in the upright position. Thus, one might expect that in patients with angina pectoris the administration of glyceryl trinitrate would result in greater improvement in exercise tolerance in the upright than in the supine posture. The present investigation was designed to study the influence of glyceryl trinitrate on exercise tolerance and circulatory changes during upright and supine exercise in patients with angina pectoris.

Methods

Sixteen male patients, aged 38 to 62 years (average 50 years), with uncomplicated, stable exercise-induced angina pectoris were studied. None had suffered a myocardial infarction, were hypertensive, or had clinical or radiological evidence of cardiac enlargement or failure. The history of angina ranged from 6 months to 7 years (average 18 months) and was induced solely and repeatedly by exercise in all patients. None suffered from nocturnal or emotionally provoked angina. None was taking drugs other than sublingual glyceryl trinitrate and the

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latter was discontinued for at least 24 hours before these studies.

The resting electrocardiogram was normal in all patients, but during exercise all developed ischaemic ST segments characterised by horizontal or downsloping ST segment depression, 0·1 mV or more of at least 0·08 seconds duration, in modified lead V5. Informed consent was obtained from each patient.

During preliminary studies, 24 to 48 hours before the definitive investigations, each patient walked on a motor driven treadmill employing the Bruce's multistage procedure (Bruce, 1971). The patients were instructed to indicate the point at which definite chest pain (P_1) occurred and the point when the pain became of moderate intensity (P_2), at which point exercise was discontinued. From these observations, patients who experienced chest pain by the end of stage 2 or the beginning of stage 3 during treadmill exercise were selected for further studies. Depending on the response during treadmill exercise, the initial workload on the bicycle ergometer was chosen and increased at 3-minute intervals aiming to induce chest pain between 4 and 7 minutes of exercise. A record of this was made and the same workloads used in the definitive studies. Such strict criteria for selection were considered necessary in order to assess the influence of posture and sublingual glyceryl trinitrate in these patients.

Precautions were taken to control factors which might have produced changes in exercise tolerance. The laboratory temperature was 20-22°C, and the patient's apprehension was reduced by familiarisation with the techniques and staff. The studies were performed each morning at the same time, in a fasting state with premedication. Patients did not smoke for 2 hours before or during the study.

In each posture, control observations were made at rest and during two periods of exercise, separated by 30 minutes (control studies 1 and 2). Each study consisted of observations at rest over a 5-minute period followed by multistage exercise. After a further 30-minute rest period, patients were given 0·6 mg sublingual glyceryl trinitrate and observations were made at rest for 5 minutes and the exercise test was repeated (study 3). The end-point during the control studies was moderate angina (P_2). After glyceryl trinitrate, attempts were made to continue exercise to P_2, but in some patients fatigue necessitated discontinuation of exercise before this end-point.

Modified lead V5 of the electrocardiogram was monitored on an oscilloscope throughout the study and records were taken on a standard electrocardiograph machine at a paper speed of 25 mm/s at 1-minute intervals for the 5-minute rest period and during exercise. Further records were taken at P_1 and P_2. The heart rate and ST segment depression in 10 consecutive beats were measured from the electrocardiogram. The blood pressure was measured by a sphygmomanometer at 1-minute intervals at rest and during exercise and also at P_1 and P_2. Detailed records of the exact time of onset of P_1 and P_2 were made separately. The rate pressure product in mmHg/min × 10^{-2} was calculated as the product of systolic arterial blood pressure and heart rate × 10^{-2}.

The order of exercise was randomised. Only one form of exercise was performed on a given day; patients were brought back on the next day and studies performed in the remaining posture.

Statistical analysis of the data was carried out using paired Student's t test or ordinary t test. Subsequent coronary angiography was carried out

Table 1 *Summary of circulatory and electrocardiographic data during two control studies*

State	*Heart rate (beats/min)*	*Blood pressure (mmHg)*		*Rate pressure product (mmHg/min × 10^{-2})*	*ECG ST depression (mm)*
		Systolic	*Diastolic*		
Standing					
C_1 Rest	83 ± 3	127 ± 3	85 ± 2	106 ± 5	0·0 ± 0·0
C_1 Ex P_1	125 ± 3	164 ± 5	79 ± 3	207 ± 8	1·1 ± 0·1
C_1 Ex P_2	133 ± 3	170 ± 5	79 ± 3	227 ± 10	1·7 ± 0·1
C_2 Rest	84 ± 3	123 ± 7	84 ± 2	104 ± 5	0·0 ± 0·0
C_2 Ex P_1	120 ± 6	159 ± 5	78 ± 3	200 ± 9	1·1 ± 0·1
C_2 Ex P_2	134 ± 4	166 ± 6	78 ± 2	223 ± 11	1·5 ± 0·1
Supine					
C_1 Rest	72 ± 2	126 ± 3	80 ± 2	90 ± 4	0·0 ± 0·0
C_1 Ex P_1	109 ± 4	160 ± 4	86 ± 2	179 ± 8	1·3 ± 0·1
C_1 Ex P_2	113 ± 4	166 ± 5	86 ± 3	187 ± 10	1·3 ± 0·1
C_2 Rest	74 ± 3	125 ± 3	81 ± 2	91 ± 4	0·0 ± 0·0
C_2 Ex P_1	113 ± 4	162 ± 4	85 ± 3	185 ± 8	1·2 ± 0·1
C_2 Ex P_2	115 ± 4	168 ± 5	84 ± 3	193 ± 10	1·2 ± 0·1

Data presented as mean ± standard error of the mean.
Abbreviations: C_1, control study 1; C_2, control study 2; Ex, exercise; P_1, onset of chest pain; P_2, moderately severe chest pain.

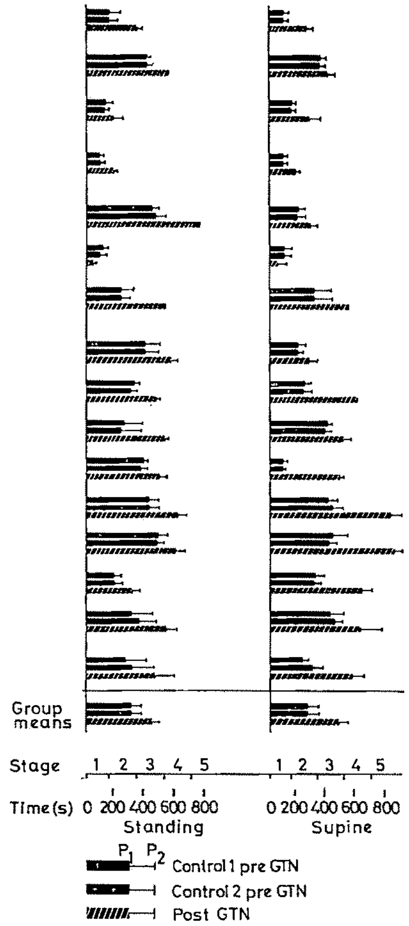

Fig. 1 *Individual and group mean values for duration of exercise before and after administration of glyceryl trinitrate. The duration of exercise to the onset of chest pain (P_1) and when the pain became of moderate severity (P_2) increased significantly after glyceryl trinitrate in both the standing and supine postures.*

in 15 of the 16 patients and showed significant (more than 75%) obstructive disease of one or more coronary arteries.

Results

CONTROL STUDIES (Table 1)

At rest, heart rate, systolic and diastolic blood pressures, and rate pressure product were similar in the same posture during the 2 control studies. All patients experienced mild (P_1) and moderate (P_2) chest pain and developed significant ST segment depression during exercise in the standing and supine positions. In each patient, in the same posture, the duration of exercise to P_1 and P_2 during the 2 control studies was similar (Fig. 1). Similarly, at both P_1 and P_2 the individual and group values for ST segment depression, heart rate, systolic and diastolic blood pressures, and rate pressure product during the 2 control periods were similar. In view of these observations, the average of the values obtained during the 2 control periods has been used for subsequent comparison (Table 2).

At rest, the average heart rate in the standing (83 ± 3 beats/min, mean ± SE) position was higher than in the supine posture (73 ± 3 beats/min) ($P < 0{\cdot}05$); systolic and diastolic blood pressure in the 2 positions were similar. The resting rate pressure product in the standing position (105 ± 5 mmHg/min × 10^{-2}) was higher than in the supine position (89 ± 4 mmHg/min × 10^{-2}) ($P < 0{\cdot}05$).

During exercise at both P_1 and P_2, the heart rate during treadmill exercise (123 ± 4 and 134 ± 4 beats/min) was significantly higher than during supine exercise (111 ± 2 and 114 ± 4 beats/min) ($P < 0{\cdot}01$). Systolic blood pressure was similar during the 2 exercise periods (treadmill P_1, 162 ± 5, P_2, 168 ± 6 mmHg; supine P_1, 161 ± 4, P_2, 167 ± 5 mmHg). Thus, because of the different heart rates in the 2 postures, higher values for rate pressure product were obtained during treadmill exercise both at P_1 (203 ± 9 mmHg/min × 10^{-2}), and P_2 (225 ± 11 mmHg/min × 10^{-2}) than during supine bicycle exercise (P_1 182 ± 8, P_2 190 ± 10 mmHg/min × 10^{-2}) ($P < 0{\cdot}01$) (Fig. 2).

STUDIES AFTER GLYCERYL TRINITRATE (Table 2)

At rest after glyceryl trinitrate, there was a significant decrease in systolic blood pressure ($P < 0{\cdot}01$), and increase in heart rate ($P < 0{\cdot}001$) from the control values in both the postures.

During both the treadmill and supine exercise after glyceryl trinitrate administration, all patients developed angina (P_1), while moderately severe angina (P_2) was experienced by 14 patients during treadmill exercise and by 12 patients during supine bicycle exercise. In the patients who did not experience P_2 after glyceryl trinitrate, exercise was discontinued primarily because of fatigue. The duration of exercise after glyceryl trinitrate to P_1 increased in all but 1 patient from the control values during each mode of exercise (Fig. 1). The average values for exercise duration after glyceryl trinitrate increased significantly from the control values during treadmill (433 ± 46 s vs 288 ± 35 s, $P < 0{\cdot}01$) and supine bicycle exercise (450 ± 56 s vs 240 ± 29 s, $P < 0{\cdot}01$) (Fig. 1).

Since every patient did not experience P_2 after

Table 2 *Summary of circulatory and electrocardiographic data before and after glyceryl trinitrate*

State	*Heart rate (beats/min)*	*Blood pressure (mmHg)*		*Rate pressure product (mmHg/min × 10^{-2})*	*ECG ST depression (mm)*
		Systolic	*Diastolic*		
Standing					
C Rest	83 ± 3	127 ± 3	84 ± 2	105 ± 5	0·0 ± 0·0
C Ex P_1	124 ± 4	162 ± 5	79 ± 3	203 ± 9	1·3 ± 0·1
C Ex P_2	134 ± 4	168 ± 6	79 ± 3	225 ± 11	1·7 ± 0·1
GTN Rest	109 ± 4*	92 ± 4*	70 ± 3*	100 ± 5	0·0 ± 0·0
GTN Ex (CP_1)	126 ± 4	151 ± 5	72 ± 4	192 ± 10	0·5 ± 0·1*
GTN Ex P_1	144 ± 4*	167 ± 6	74 ± 3	242 ± 14*	1·2 ± 0·1
GTN Ex P_2	147 ± 4*	167 ± 6	79 ± 4	248 ± 13*	1·5 ± 0·1
Supine					
C Rest	73 ± 3	126 ± 3	81 ± 2	89 ± 4	0·0 ± 0·0
C Ex P_1	111 ± 2	161 ± 4	86 ± 3	182 ± 8	1·1 ± 0·1
C Ex P_2	114 ± 4	167 ± 5	85 ± 3	190 ± 10	1·3 ± 0·1
GTN Rest	85 ± 3*	118 ± 3*	81 ± 3	97 ± 4	0·0 ± 0·0
GTN Ex (CP_1)	112 ± 4	165 ± 4	83 ± 3	185 ± 9	0·8 ± 0·1*
GTN Ex P_1	119 ± 7*	181 ± 6*	84 ± 3	230 ± 11*	1·0 ± 0·1
GTN Ex P_2	127 ± 4*	185 ± 5*	86 ± 4	235 ± 11*	1·1 ± 0·2

Data presented as mean ± standard error of the mean.
Abbrevations: C, average of 2 control studies 1 and 2; Ex, exercise; GTN, glyceryl trinitrate; GTN Ex (CP_1), identical work loads as during control studies at P_1; P_1, onset of chest pain; P_2, moderately severe chest pain; *, $P < 0·01$ in comparison with the corresponding control values.

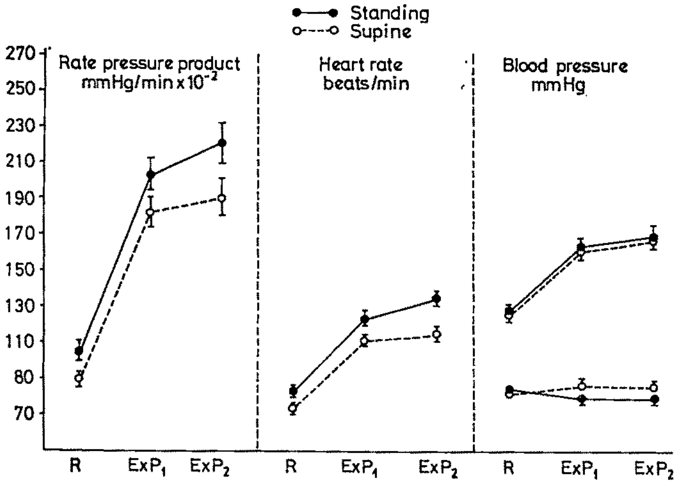

Fig. 2 *Group mean ± SEM values for rate pressure product, heart rate, and systolic and diastolic blood pressure at rest (R) and during exercise (Ex) in the standing and supine postures. Heart rate and rate pressure product were significantly higher in the standing position at rest (R) and during exercise at the onset of angina (P_1) and when angina became of moderate intensity (P_2).*

glyceryl trinitrate administration, the exercise duration to fatigue was substituted for P_2 and the group values so obtained were compared with control readings at P_2. Thus, after glyceryl trinitrate at P_2, exercise tolerance was significantly increased in each posture (treadmill, 462 ± 43 s vs 357 ± 35 s, $P < 0·01$); (supine, 500 ± 57 s vs 297 ± 33 s, $P < 0·001$).

In comparison with the control studies, the majority of patients exercised to higher work loads after glyceryl trinitrate administration in each posture. Thus, the individual and group values for rate pressure product at P_1 after glyceryl trinitrate were significantly higher than the control values at P_1 during the two modes of exercise (treadmill, 242 ± 14 vs 203 ± 9 mmHg/min × 10^{-2}, $P < 0·001$; supine, 230 ± 11 vs 182 ± 8 mmHg/min × 10^{-2}, $P < 0·001$) (Fig. 3a and b). The increase in rate pressure product during treadmill exercise was the result of a higher heart rate (144 ± 4 vs 123 ± 4 beats/min, $P < 0·001$) while the systolic blood pressure was similar to the control values (167 ± 6 vs 162 ± 5 mmHg) (Fig. 3a). In the supine position after glyceryl trinitrate, the increase in rate pressure product was the result of both a higher heart rate (119 ± 7 vs 111 ± 2, $P < 0·001$), and systolic blood pressure (181 ± 6 vs 161 ± 4, $P < 0·001$), than during the control exercise period (Fig. 3b). ST depression at P_1 was similar before and after glyceryl trinitrate (Fig. 4).

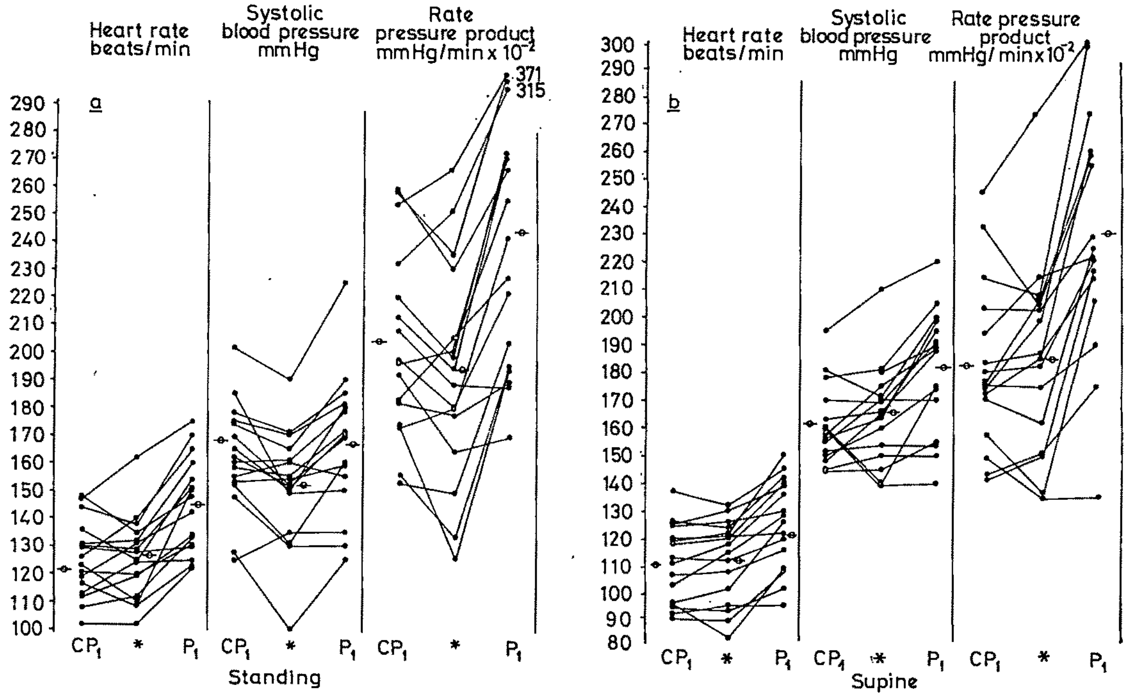

Fig. 3a and b *Individual* (⊙) *and group mean* (-⊖-) *values for heart rate, systolic blood pressure, and rate pressure product before and after administration of glyceryl trinitrate. In both postures, at the onset of chest pain* (P_1) *rate pressure product increased significantly after glyceryl trinitrate in comparison with the control* (*C*) *values. The increase in rate pressure product was due to higher heart rate during standing exercise and both the higher heart rate and systolic blood pressure during supine exercise. However, at the same work loads* (*) *after glyceryl trinitrate, there was no significant change in rate pressure product after glyceryl trinitrate in comparison with the values at* P_1, *during the control* (*C*) *studies in either posture before glyceryl trinitrate.*

The values for rate pressure product at P_2 after glyceryl trinitrate were also significantly higher than the values during exercise before glyceryl trinitrate in the two positions (treadmill, 248 ± 13 vs 225 ± 11 mmHg/min × 10^{-2}, $P < 0{\cdot}001$; supine, 235 ± 11 vs 190 ± 10 mmHg/min × 10^{-2}, $P < 0{\cdot}001$). Again these differences were the result of higher heart rate in the upright position and of both a higher heart rate and systolic blood pressure during supine exercise.

Despite the fact that in the control studies patients could exercise to a higher rate pressure product in the upright posture, after glyceryl trinitrate, the increase in rate pressure product seen during exercise was similar in each position.

While the rate pressure product at the onset of angina (P_1) was higher after glyceryl trinitrate in each position, it was observed that at the same work load the group mean rate pressure products were similar before and after glyceryl trinitrate (Fig. 3a and b). Thus, when the rate pressure product at P_1 before glyceryl trinitrate was compared with the rate pressure product at the same work load after glyceryl trinitrate, there was no significant difference in either position (treadmill, 192 ± 10 vs 203 ± 9; supine, 185 ± 9 vs 182 ± 8 mmHg/min × 10^{-2}). Examination of individual values of rate pressure products at identical work loads before and after glyceryl trinitrate showed that the values were lower in 11 during treadmill exercise and in 5 patients during supine bicycle exercise after administration of glyceryl trinitrate. At this time, ST segment depression was less after glyceryl trinitrate than the control values (treadmill, 0·5 ± 0·1 vs 1·3 ± 0·1 mm; supine 0·8 ± 0·1 vs 1·1 ± 0·1 mm) ($P < 0{\cdot}05$) (Fig. 4).

Discussion

The present study shows that patients with coronary artery disease were able to exercise to higher rate pressure products at angina in the upright posture

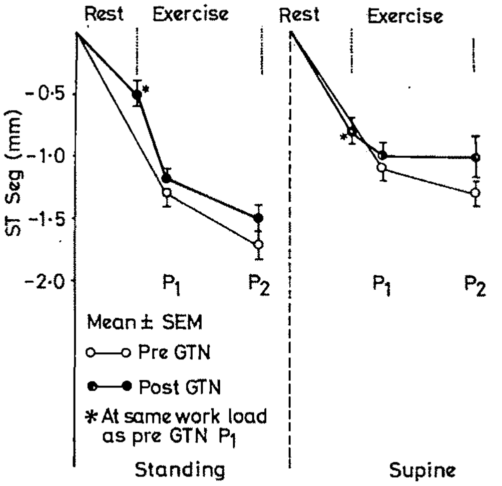

Fig. 4 *Changes in ST segment depression from rest to exercise during mild* (P_1) *and moderate* (P_2) *angina. In each posture at the same work loads, ST segment depression was significantly reduced after glyceryl trinitrate (GTN) in comparison with the values at* P_1 *during studies before glyceryl trinitrate.*

than in the supine position. Despite these postural differences, sublingual glyceryl trinitrate increased exercise tolerance and rate pressure product at the onset of angina by a similar degree in both positions.

Before the above results can be put into proper perspective, the methods used must be considered. Measurement of blood pressure by sphygmomanometry rather than by direct arterial cannulation could have introduced errors, but all determinations were made by the same observer and each patient acted as his own control. In the present study, blood pressure recordings during rest and exercise by sphygmomanometry were reproducible during the control studies in each patient. The noninvasive measurement of blood pressure is the only practical way in studies such as this where repeated observations are performed on different days. A close approximation has been documented between systemic arterial pressure recorded by arterial cannulation and sphygmomanometry (Nelson *et al.*, 1974; Clausen and Trap-Jensen, 1976).

It has been reported that normal subjects can exercise to similar work loads and heart rates during exercise in the supine and upright positions (Bevegård *et al.*, 1960, 1963; Epstein *et al.*, 1969). In contrast to this, in the present study, patients with coronary artery disease were able to exercise to higher heart rates and rate pressure products in the upright posture before the onset of chest pain. These findings are in agreement with three previous reports (Lecerof, 1971; Bygdeman and Wahren, 1974; Thadani *et al.*, 1977). On the other hand, Robinson (1967) reported that patients with coronary artery disease invariably experienced angina at constant heart rate and systolic blood pressure products. Robinson (1967) also reported that in some situations it was necessary to correct the rate pressure product for changes in the systolic ejection period, and he found that in the upright position angina occurred in each individual at a constant corrected rate pressure product despite different modes of exercise. Robinson (1967), however, did not compare the uncorrected or corrected rate pressure product at angina in the supine and upright postures as was done in the present study. We did not measure the ejection period in the present study and hence have not made corrections for this, but Bygdeman and Wahren (1974) reported that both the rate pressure product and triple product at angina were significantly higher during sitting than supine bicycle exercise.

Before considering the possible mechanisms responsible for the differences in exercise tolerance and rate pressure product at angina during exercise in the supine and upright postures, it is important to examine the pathophysiology of angina and myocardial ischaemia. In patients with coronary artery disease, angina pectoris occurs when the myocardial oxygen demand exceeds oxygen supply. The three important haemodynamic variables directly related to myocardial oxygen requirements are: (1) intramyocardial tension (a function of ventricular systolic pressure, radius, and wall thickness), (2) heart rate, and (3) the contractile state of the ventricle (Sarnoff *et al.*, 1958; Sonnenblick *et al.*, 1965; Boerth *et al.*, 1969). Interplay of these factors determines the net oxygen demand.

There is evidence to suggest that in normal subjects both at rest and during exercise, the heart volume is smaller in the sitting than in the supine posture (Holmgren and Ovenfors, 1960). Furthermore, the results from our laboratory have shown that in patients with coronary artery disease, left ventricular filling pressures were significantly lower during sitting than supine bicycle exercise at the onset of angina (Thadani *et al.*, 1977). It is therefore probable that the higher rate pressure product achieved during upright exercise at the onset of angina is the result of decreased ventricular volume which is a major determinant of intramyocardial tension.

In the present study, sublingual glyceryl trinitrate resulted in more distinct reduction in resting systolic blood pressure in the standing than in the supine position. This was responsible for a more pronounced reflex increase in heart rate in the standing position. However, during exercise, glyceryl trinitrate resulted in a similar increase in exercise tolerance and rate pressure product at angina in the two postures. Previous reports on the effect of glyceryl trinitrate on rate pressure product at angina have been variable. Robinson (1968) and Clausen and Trap-Jensen (1976) reported that rate pressure product at angina was similar before and after sublingual triglyceryl trinitrate. However, Detry and Bruce (1971) and Goldstein *et al.* (1971) reported the rate pressure product at angina to be significantly higher than during exercise before glyceryl trinitrate. In the present study and in that of Detry and Bruce (1971), blood pressure was measured by sphygmomanometry, but Robinson (1968) and Goldstein and colleagues (1971) recorded the blood pressure by direct intra-arterial cannulation. It is, therefore, unlikely that this reported discrepancy in rate pressure product at angina after glyceryl trinitrate is the result of different methods used for recording the blood pressure in the different studies.

Rate pressure product does not take ejection time into consideration. Robinson (1968) and Goldstein and colleagues (1971) compared the triple product of heart rate, systolic blood pressure, and ejection time at angina before and after glyceryl trinitrate and reported no change in this product after glyceryl trinitrate. However, other workers have shown that the rate pressure product and heart rate alone are better correlates of oxygen consumption than either the tension time index or triple product, especially after drug intervention (Kitamura *et al.*, 1972; Jorgensen *et al.*, 1973; Nelson *et al.*, 1974). In the present study, after glyceryl trinitrate, the rate pressure product and heart rates were similar to control values at identical work loads but as the majority of patients exercised to higher work loads after glyceryl trinitrate before experiencing angina, this product was significantly higher at angina after glyceryl trinitrate. The increase in rate pressure product at angina after glyceryl trinitrate during treadmill exercise was primarily the result of the higher heart rate, while during supine exercise the increase in this product was caused by both higher heart rate and systolic blood pressure.

Heart rate and systolic blood pressure are important determinants of myocardial oxygen requirements but these two variables do not take into account the influence of ventricular volume and myocardial contractility, factors that are important determinants of myocardial oxygen requirements. In the present study, similar rate pressure products were reached during exercise at identical work loads before and after glyceryl trinitrate. However, when exercise was continued to angina, the rate pressure product at this point was greater than at angina before glyceryl trinitrate administration. This improvement in exercise tolerance after glyceryl trinitrate could be the result of either (1) improved coronary perfusion to ischaemic myocardial zones or (2) diminished left ventricular volume which would reduce ventricular wall tension and myocardial oxygen demand for a given rate pressure product.

The effects of glyceryl trinitrate on the distribution of coronary blood flow in man remains uncertain. In normal subjects, this drug has been shown to increase coronary blood flow by reducing impedance to coronary flow but in patients with obstructive lesions in the coronary arteries, the majority of the studies have failed to show an increase in coronary flow in the diseased vessels (Gorlin *et al.*, 1959). On the other hand, glyceryl trinitrate has been shown to increase the collateral blood flow to the ischaemic myocardium (Forman *et al.*, 1973; Goldstein *et al.*, 1974). However, at times this drug may aggravate ischaemia through a steal phenomenon (Rowe, 1970). The effects of glyceryl trinitrate on left ventricular volume have been more consistent. The drug, by its effects on venous and arteriolar dilatation, reduces resting ventricular volume in both the supine and upright postures (Williams *et al.*, 1965; Hoeschen *et al.*, 1966; Burggraf and Parker, 1974). In a recent echocardiographic study, glyceryl trinitrate reduced ventricular volume during sitting bicycle exercise (Goldstein *et al.*, 1977). Glyceryl trinitrate consistently reduces left ventricular diastolic pressure at rest and during exercise (Parker *et al.*, 1971), and this should facilitate subendocardial perfusion.

Although one might expect the upright posture to be associated with greater changes in left ventricular volume, the improvement in exercise tolerance and increase in rate pressure product after glyceryl trinitrate were similar during both upright and supine exercise. This could be interpreted as evidence for the predominant influence of glyceryl trinitrate on coronary perfusion but it is possible that similar changes in ventricular volume occurred in both positions. The design of the present noninvasive study does not permit us to differentiate the importance of these mechanisms.

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Excretion of myoglobin in urine after cardiac catheterisation

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SUMMARY Myoglobin levels were assayed in each urine specimen voided during 12 hours before and 48 hours after routine cardiac catheterisation in 146 patients using an indirect haemagglutination method detecting concentrations in excess of 0·015 mg/ml. Myoglobinuria was found in only one patient before but in 39 patients after cardiac catheterisation (27%), either in the first (34 patients) or the second (5 patients) post-catheterisation urine sample. Once detected, myoglobin was present in all subsequent urine specimens for the next 3 to 22 hours (mean 11·8 hours). The mean amount excreted ± SE was 14·0 ± 1·6 mg (range 2·6 to 30 mg) excluding the one patient with myoglobinuria before catheterisation. This patient, who had severe aortic stenosis and atherosclerotic heart disease, excreted 130 mg myoglobin. Patients with myoglobinuria required longer screening time to complete the procedures undertaken than those in whom myoglobin was not detected—15·6 ± 1·4 and 11·1 ± 0·6 minutes, respectively (means ± SE: $P < 0·01$).

We conclude that myoglobinuria is not uncommon after cardiac catheterisation, and that though the myoglobin detected may be released from skeletal muscle, it could be partly or wholly of cardiac origin and indicate transient, and presumably reversible, myocardial injury.

When muscle is damaged it releases myoglobin into the bloodstream and this is then rapidly excreted in the urine (Kagen, 1973). We have recently developed a simple and sensitive assay for urinary myoglobin (Cloonan *et al.*, 1976) and have used it to quantify myoglobinuria after acute myocardial infarction (Donald *et al.*, 1977). In the course of evaluating the significance of myoglobinuria, we sought evidence for this after a number of cardiovascular investigations. We report here the unexpected finding of substantial amounts of myoglobin in the urine in 27 per cent of patients undergoing cardiac catheterisation.

Subjects and methods

Investigations were done on 146 patients coming to routine cardiac catheterisation to test for myoglobinuria during the 12 hours before and the 48 hours after the procedure. The diagnoses are shown in Table 1. The volume of each urine specimen voided was recorded and aliquots of each specimen were immediately frozen at −20°C and later tested for the presence of myoglobin using an indirect haemagglutination method. With this method, the presence of myoglobin in the urine is detected by inhibition of agglutination of sensitised red blood cells; myoglobin reacts with the specific antibody before the addition of the cells. The method detects a minimum myoglobin concentration of 0·02 mg/ml and has been described fully elsewhere (Cloonan *et al.*, 1976).

Approximately 1 hour before cardiac catheterisation each patient received an intramuscular injection of either diazepam (0·14 mg/kg) or papaveretum (0·14 mg/kg) and hyoscine hydrobromide (0·03 mg/kg). Most patients with valvular heart disease (22 of 30—Table 1) received in addition an intramuscular injection of crystalline penicillin (2 million units) 1 hour before and 6 hours after cardiac catheterisation. The catheter study was performed by one of three experienced cardiologists using either a right brachial vessel cut-down or a percutaneous right femoral puncture approach. The procedures undertaken are shown in Table 1. Indocyanine Green Dye USP (6 ml injection) was used to measure cardiac output. The contrast material for angiography was Urografin 76

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Table 1 *Diagnoses, premedication, and procedures undertaken, and incidence of myoglobinuria*

Variables	*No. of patients*	*No. myoglobin positive*	%
(1) *Diagnosis*			
Normal	25	4	16
Coronary artery disease	92	28	30
Valvular heart disease	30*	7†	23
Miscellaneous	11	4‡	36
(2) *Premedication*			
Papaveretum and hyoscine hydrobromide (P and H)	89	31	34
Diazepam (D)	54	8	15
Penicillin plus P and H or D	22	5	23
Other	4	2	—
(3) *Procedure*			
Cut-down	136	35	26
Percutaneous	19	3	16
Right heart catheter (RHC) only	8	2	25
Left heart catheter (LHC) only	10	4	40
RHC and LHC	127	33	26
Selective coronary angiogram	120	35	29
Aortogram	15	3	20
Left ventricular angiogram	130	35	27
Indocyanine green dye given	91	33	36
Pulmonary angiogram	3	2	—
Other	7	1	14

*Includes 12 with associated coronary artery disease.
†Includes 4 with associated coronary artery disease.
‡Two patients with hypertrophic obstructive cardiomyopathy, 1 with a congestive cardiomyopathy and 1 with a conduction disturbance.

(Schering). We recorded the image intensification screening time required for each patient and used this to estimate the amount of catheter manipulation within the great arteries, veins, and the cardiac chambers during the procedure. The Sones technique was used for all coronary angiograms.

Twelve-lead electrocardiograms were performed routinely the day before and the day after cardiac catheterisation. In 45 of the 146 patients, serum creatine kinase and hydroxybutyrate dehydrogenase estimations were performed 24 to 30 hours before catheterisation and 18 to 24 hours after. Both were estimated kinetically at 37°C and 340 nm wave length using 'Calbiochem' reagents. 'Calbiochem' Stat-Pack (catalogue No. 869214) was used for creatine kinase. Student's t test and χ^2 analysis were used in the statistical calculations. Differences were accepted as significant when P was less than 0·05.

Results

Myoglobinuria was detected after cardiac catheterisation in 39 (27%) of the 146 patients studied. It was not found in any of the patients during the 12-hour period before catheterisation, with one exception (see below). The distribution of the myoglobin-positive patients in relation to diagnosis, the intramuscular premedication given, the procedures undertaken, and the complications are shown in Tables 1 and 2.

Table 2 *Complications after catheterisation and incidence of myoglobinuria*

Complications	*No. of patients*	
	Myoglobin positive	*Myoglobin negative*
Lost pulse/pulse problems	1	5
Arrhythmia requiring treatment	2	2
Hypotension requiring pressor agents	0	2
Haematoma formation	0	1

There was a constant pattern of excretion in those patients with myoglobinuria. Fig. 1 illustrates this in one patient. Myoglobin was excreted in the first 7 urine samples passed during the first 18 hours after cardiac catheterisation but was not found thereafter. The small arrows indicate urine specimens in which myoglobin was not detected. This patient excreted a total of 30 mg myoglobin.

In 34 of the 39 myoglobin-positive patients, myoglobin was detected in the first urine specimen after cardiac catheterisation; in the remaining 5 it was present for the first time in either the second or third post-catheter specimen. Once detected, myoglobin was present in all subsequent urine specimens for the next 3 to 22 hours (mean 11·8 hours). Excluding the one patient in whom myoglobinuria was detected before catheterisation, the mean amount of myoglobin excreted ± SE was 14·0 ± 1·6 mg, with a range of 2·6 to 30·0 mg.

Fig. 2 shows the data obtained during two studies in one patient. The first study in this patient was incomplete. Right heart catheterisation was performed through a cut-down on the right brachial

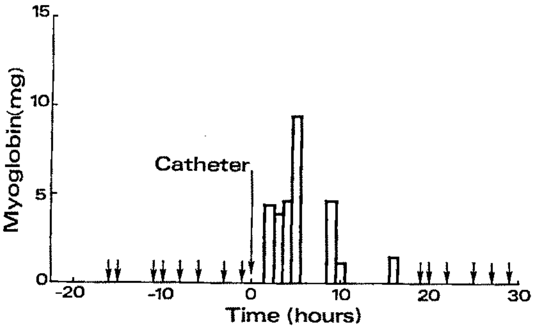

Fig. 1 *Relation between amount of myoglobin excreted in each urine specimen and time before and after cardiac catheterisation (zero time) in one patient. Arrows indicate urine samples in which myoglobin was not detected. Myoglobin was detected in the first post-catheter urine specimen and in each subsequent specimen until 16 hours after catheterisation. In all, 30 mg myoglobin was excreted.*

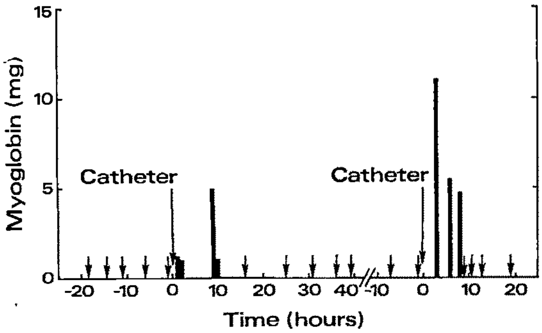

Fig. 2 *Relation between amount of myoglobin excreted in each urine sample and time before and after cardiac catheterisation (zero time) in a patient who had two cardiac catheterisations within 3 days. Arrows indicate urine specimens in which myoglobin was not detected. Twelve milligrams of myoglobin were excreted after the first catheterisation and 25 mg after the second (a more extensive study—see text).*

vein. Left heart catheterisation and coronary angiography were attempted via a right brachial artery cut-down, but the study had to be abandoned because of technical difficulty experienced in passing the catheter from the right brachial artery into the ascending aorta. A right coronary artery angiogram only was performed, and 12 mg myoglobin was excreted after this procedure (Fig. 2). A complete study was obtained 3 days later from the left arm using a brachial artery cut-down. The left heart was catheterised and left ventriculography as well as selective coronary angiograms and an aortogram were performed. This established that the patient had hypertrophic obstructive cardiomyopathy with moderate mitral and aortic regurgitation and normal coronary arteries. The screening time required was 29 minutes. After this second catheterisation 25 mg myoglobin was excreted.

The screening time in the myoglobin-positive patients was 15·6 ± 1·4 minutes (mean ± SE) whereas it was significantly less in those in whom it was not detected (11·1 ± 0·6 minutes; $P < 0{\cdot}01$).

From Table 1 it can be seen that the finding of myoglobinuria was not closely related to either diagnosis, the type of premedication, or the procedure undertaken. However, the incidence was highest in those patients with coronary artery disease whose studies routinely included a brachial artery cut-down, a combination of left and right heart catheterisation, coronary angiography, and left ventricular cine angiography. But there was no relation between the severity of coronary artery disease and the incidence of myoglobinuria among these 92 patients (χ^2 analysis). Eleven had less than 70 per cent obstructions of major coronary vessels and of these 3 had myoglobinuria; the other 81 patients had greater than 70 per cent obstructions and of the 24 with single vessel disease 9 had myoglobinuria, whereas 8 of the 26 with two vessel disease and 8 of the 31 with three vessel disease had myoglobinuria. Nor was there any significant relation between the amount of myoglobin excreted in the urine and the extent of coronary artery disease assessed by the number of vessels affected or myocardial function as judged by the ejection fraction measured from ventriculograms (χ^2 analysis).

In no patient was there any change in the electrocardiogram during the 48 hours after catheterisation to suggest evidence of cardiac muscle damage. The incidence of myoglobinuria was not influenced by the cardiologist performing the catheterisation (χ^2 analysis). It occurred in 10 of 45 patients (22%) studied by the first, 17 of 62 patients studied by the second (27%), and 10 of 30 patients studied by the third (33%); the remaining 7 patients were studied by experienced fellows in cardiology and myoglobinuria occurred in 2 (28%). In 6 of the 146 patients, diminished or transiently absent pulses occurred distal to the brachial artery cut-down. But of these, there was only one among the myoglobin-positive patients (see below); in the other 5 patients, myoglobinuria was not detected (Table 2). The other post-catheter complications did not occur more frequently in the myoglobin-positive patients (Table 2).

Among the 8 myoglobin-positive patients in whom pre- and post-catheterisation enzyme estimations were available, values for hydroxybutyrate dehydrogenase were the same—139 ± 22 and 135 ± 27 IU/litre (means ± SE), respectively—while there was a small but statistically insignificant (paired t test) increase in creatine kinase after catheterisation from 32 ± 8 to 51 ± 16 IU/litre (means ± SE) and with the small numbers there was no significant relation in individual patients between the change in creatine kinase and the amount of myoglobin excreted. The enzyme values before and after catheterisation in the myoglobin-negative patients were virtually identical for both enzymes measured.

The patient with pre-catheter myoglobinuria was a 68-year-old woman with severe aortic stenosis but without recent or past history of chest pain suggesting myocardial ischaemia. The pre-catheter urine sample was passed at 6.30 a.m. and contained 12·5 mg myoglobin. She had had no intramuscular injections before this. The study confirmed the severity of the stenosis (calculated valve area = 0·5 cm^2) and demonstrated obstructions high in the anterior descending branch of the left coronary artery (90%) and in the middle third of the right coronary artery (70%) with good left ventricular function. Screening time was 32½ minutes and, at the end, the right radial pulse was reduced, the pressure index (right radial divided by left radial systolic pressure) being 0·68. Exploration of the brachial artery was not thought to be indicated. She was not hypotensive at any time after catheterisation.

Myoglobin was detected in each of the first 5 post-catheter urine specimens passed, totalling in all 130 mg myoglobin including the pre-catheter sample. It was not detected in subsequent urine samples. The pre-catheter electrocardiogram showed extreme left ventricular hypertrophy with symmetrical ST segment depression and T wave inversion and was unaltered after catheterisation. Unfortunately, there were no measurements of pre- and post-catheterisation serum enzymes. At no time did she complain of pain suggesting myocardial ischaemia. Successful operation was later undertaken with replacement of the aortic valve and the insertion of a bypass graft to the left anterior descending coronary artery.

Discussion

So far as we are aware, this is the first report of myoglobinuria following cardiac catheterisation. Since myoglobin was detected in approximately 1 in every 4 patients submitted to this procedure, and the amounts excreted were substantial (mean 14·0 mg; range 2·6 to 30·0 mg), the mechanisms involved become particularly important.

As the method of measuring myoglobin in the urine does not distinguish between that of cardiac or skeletal muscle origin, myoglobin could have been released from either or from both types of muscle. It seems unlikely that intramuscular injections given as premedication contributed to the myoglobin release. This possibility was explored fully during an earlier study in which 15 patients were given intramuscular injections similar to those in the present study. The same method for estimating myoglobin was used and in no patient was myoglobinuria detected (Cloonan *et al.*, 1976). Moreover, in the present study, the incidence of myoglobinuria in the patients with valvular heart disease tended to be relatively low (see Table 1) despite these patients receiving intramuscular injections of 2 million units of penicillin 1 hour before and 6 hours after the procedure in addition to routine premedication. We concluded, therefore, that muscle damage resulting from intramuscular injections was not responsible for the myoglobinuria. Skeletal muscle ischaemia secondary to vessel occlusion by catheters may have been a factor even though transient loss or reduction of the radial pulse after the procedure occurred in only one myoglobin-positive patient whereas this was seen in 5 patients negative for myoglobinuria. Furthermore, no episodes of hypotension or haematoma formation were recorded in the myoglobin-positive group whereas there were 2 of the former and 1 of the latter among the negative patients (Table 2). It is quite likely, therefore, that the myoglobin was partly or wholly of cardiac origin. Heart muscle has a much higher myoglobin content than does skeletal muscle (Kagen, 1973).

Myoglobin is a relatively small molecule (molecular weight 17 000), much smaller than the enzymes commonly used as indicators of myocardial damage, and it may move more easily through damaged cell membranes than, for example, creatine kinase or hydroxybutyrate dehydrogenase. It is noteworthy that myoglobinuria was detected principally in patients with ischaemic heart disease who had coronary and left ventricular angiograms and that, as a group, the myoglobin-positive patients required significantly longer screening time to complete the procedures undertaken. This suggested that the presence and magnitude of myoglobinuria was related to the length of the procedure and to the amount accomplished during it. Thus, myoglobin of cardiac origin could have resulted from endocardial trauma by catheters, high pressure injections of contrast material, or from brief myocardial ischaemia caused by catheter occlusion of coronary arteries or dye-filled coronary arteries. Furthermore, it is possible that radio-opaque dye in coronary arteries causes transient cell membrane dysfunction leading to leakage of myoglobin from the cell. We have no explanation for the recent data of Stone and his associates (Stone *et al.*, 1977) who reported no significant increase in serum myoglobin levels in 9 patients after cardiac catheterisation. But, in view of the incidence of myoglobinuria we found (27%), changes may have been seen if more patients had been studied.

A number of authors have described an increase in serum enzyme activity—principally of creatine kinase—in a proportion of patients after cardiac catheterisation (Marpole *et al.*, 1968; Michie *et al.*, 1970; Chahine *et al.*, 1974). In the present study there was a small increase in creatine kinase in the 8 myoglobin-positive patients for whom measurements were available—from 32 ± 8 to 51 ± 16 IU/litre (means ± SE). However, with these small numbers the difference was not statistically significant; nor was there a relation in individual patients between the change in creatine kinase and the amount of myoglobin excreted. Nevertheless, it may be relevant that no increase in creatine kinase occurred in the larger number (35) of myoglobin-negative patients for whom there were enzyme measurements.

There is dispute on the origin of increased post-catheter creatine kinase. Roberts and his associates (Roberts *et al.*, 1975) measured serum activity before and after cardiac catheterisation of total creatine kinase as well as its MB isoenzyme which is found primarily in heart muscle. While peak total serum creatine kinase increased after catheterisation, the MB isoenzyme activity remained within normal limits. They concluded that the increase was not of cardiac origin.

However, in a recent study, Hori and his associates (Hori *et al.*, 1976) described differences in total serum creatine kinase increases after catheterisation between patients who did and did not have selective coronary angiography and reported further that the patients with more extensive coronary vascular disease produced larger increases in serum creatine kinase after catheterisation. Our data are not in accordance with the latter observation in that in our study the extent of coronary vascular disease and variations in ejection fraction did not correlate with the amount of myoglobin excreted. Hori and his associates (Hori *et al.*, 1976) suggested that the raised levels represented some form of myocardial damage which is much less than that seen during acute myocardial infarction. In this context, the total amount of myoglobin excreted in the present study—14·0 ± 1·6 mg—was considerably less than the 50·7 ± 9·4 mg ($P < 0{\cdot}001$) we obtained recently in 14 patients with uncomplicated acute myocardial infarction; and this latter amount was undoubtedly an underestimation since in 2 of the 14 patients the end-point of the excretion phase was not determined (Donald *et al.*, 1977). There is, therefore, probably about a fourfold difference in excretion in the two situations. Roberts and his associates (Roberts *et al.*, 1975) found a similar difference in serum creatine kinase enzyme activity after catheterisation and myocardial infarction. Since MB isoenzyme activity is only about 10 per cent of total activity the expected increase in the MB isoenzyme after catheterisation would be small if the creatine kinase increase were partly or wholly of cardiac origin. This might not be detected by comparing group mean values which could still remain within the normal range.

In the extreme case in the present series of the patient with pre-catheter myoglobinuria, we concluded that the large amount she excreted—130 mg—was almost certainly largely of cardiac origin. In an earlier study (Cloonan *et al.*, 1976) we examined random urine samples in 146 control patients. Only 4 were positive for myoglobinuria and each had an adequate medical or surgical reason for skeletal muscle damage to explain this. Our present patient had critical aortic stenosis with paroxysmal nocturnal dyspnoea, a haemodynamic situation likely to produce subendocardial ischaemia (Buckberg *et al.*, 1972). She had, furthermore, 70 per cent and 90 per cent obstructions in two of her three main coronary arteries. We suggest that, before catheterisation, she had undetected subendocardial ischaemia with release of myoglobin which became accentuated as a result of cardiac catheterisation and selective coronary angiography. Though she did have a reduced radial pulse after the procedure, this was also noted in 5 other patients in the series and all were myoglobin-negative. The amount of myoglobinuria in this patient was of a similar order to that we have found in some patients with acute myocardial infarction (Donald *et al.*, 1977).

In conclusion, we found substantial myoglobinuria in approximately 1 in 4 patients coming to routine cardiac catheterisation. It is considered likely that at least some of this myoglobin was of myocardial origin, and was related to transient and presumably completely reversible cardiac injury occurring during catheterisation and selective angiography. It seems prudent to maintain a continuing vigilance in assessing the indications for cardiac catheterisation, particularly in those patients with ischaemic heart disease in whom coronary angiography is contemplated.

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Incidence of ventricular arrhythmias in first year after myocardial infarction[1]

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SUMMARY The incidence of ventricular arrhythmias in the first year after acute myocardial infarction was studied prospectively using 24-hour Holter electrocardiogram tape monitoring. Of 108 patients who entered the trial, 74 completed the 12 months of study. Patients were initially studied at 2 weeks after infarction then at 3-monthly intervals. Ventricular premature beats were observed in 80 per cent of studies, with these arrhythmias occurring in 57 per cent of the total hours studied. 'Significant' ventricular arrhythmias defined as ventricular premature beats greater than 1 in 10 beats, multifocal ventricular premature beats, bigeminy or trigeminy, salvos (2 or 3 consecutive ventricular premature beats), R on T, or ventricular tachycardia (4 or more ventricular premature beats), occurred in 54 per cent of studies, with these arrhythmias occurring in 40 per cent of the total hours studied. The incidence of ventricular arrhythmias remained fairly constant for each 3-month period while the percentage of total studied hours for which ventricular arrhythmias occurred was significantly higher after the entry study at 2 weeks.

The incidence of ventricular arrhythmias was significantly higher in patients with inferior or posterior infarction after the entry study compared with those with anterior infarction ($P < 0{\cdot}005$). Patients who had cardiac failure in the coronary care unit or a peak serum aspartate aminotransferase > 200 IU/l had a higher long-term incidence of ventricular arrhythmias ($P < 0{\cdot}01$).

Four deaths occurred during the study. In all cases ventricular premature beats were observed on at least 1 period of study, with significant ventricular premature beats in 2 of the 3 patients who died suddenly.

A control group of 21 normal subjects had a random 24-hour Holter study and were found to have a significantly lower incidence of ventricular arrhythmias when compared with the post-infarction group. Ventricular premature beats were observed in 48 per cent of cases ($P < 0{\cdot}005$) for 28 per cent of the total hours studied ($P < 0{\cdot}025$) and significant ventricular arrhythmias in 19 per cent of cases ($P < 0{\cdot}005$) for 35 per cent of the total hours studied.

The standard electrocardiogram proved to be a poor indicator of the true incidence of ventricular premature beats found on 24-hour Holter monitoring, with 75 per cent of patients having ventricular arrhythmias and 43 per cent showing 'significant' ventricular arrhythmias when all standard electrocardiograms showed no ventricular premature beats.

In patients with coronary artery disease 60 per cent of the deaths are sudden (Kuller, 1966). The major mechanism of death is thought to be ventricular fibrillation associated with ischaemia (Lown and Wolf, 1971; Schaffer and Cobb, 1975), since most findings at necropsy show evidence of significant coronary artery disease without evidence of recent infarction (Schwartz and Walsh, 1971; Schaffer and Cobb, 1975). The magnitude of this problem has led to repeated attempts to define factors that might predict those patients at greatest risk, so that the prophylactic use of long-term antiarrhythmic agents could be considered. The presence of ventricular premature beats in patients with coronary artery disease appears to be one such factor and studies by Chiang *et al.* (1969), Hinkle *et al.* (1969), Coronary Drug Project Research Group

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(1973), and Kotler *et al.* (1973) have all shown an increased risk of sudden death in this group.

Holter continuous electrocardiogram monitoring (Holter, 1957) has been of particular value in the assessment of arrhythmias in ambulatory patients (Bleifer *et al.*, 1974). A standard 12 lead electrocardiogram tracing over 1 minute detects ventricular premature beats in 8 per cent of patients with coronary artery disease, while 12 hours of Holter monitoring in the same group shows ventricular premature beats in 62 per cent of patients (Lown and Wolf, 1971). Thus Holter monitoring is a valuable tool in defining the incidence of ventricular premature beats in a high risk population such as patients after acute myocardial infarction (Lown and Wolf, 1971).

The aims of the present study were to assess the incidence of ventricular arrhythmias in the first year after myocardial infarction and to note any change in pattern during this period. The effect of infarct site and size on the incidence of these arrhythmias was also evaluated.

Subjects and methods

A prospective study was performed using Holter 24-hour electrocardiogram tape monitoring to assess the incidence of ventricular arrhythmias in the first year after acute myocardial infarction. Patients were initially studied while ambulatory in hospital at approximately 14 days (range 7 to 24 days) after acute infarction (entry study), and had repeat 24-hour Holter monitoring at 3-monthly intervals for 1 year. A clinical examination and standard 12 lead electrocardiogram were performed at each 3-monthly review, with chest radiographs at 3 months, 6 months, and 12 months.

A 24-hour Holter study was performed in a group of normal subjects to assess the incidence of ventricular arrhythmias in the general population.

'Significant' ventricular arrhythmias were defined as ventricular premature beats (VPB) more frequent than 1 in 10 normal beats (VPB > 1 in 10), ventricular bigeminy or trigeminy, multifocal VPB, salvos (2 or 3 consecutive VPB), R on T phenomenon (R wave interrupting the preceding T wave), and ventricular tachycardia (4 or more consecutive VPB). 'Non-significant' ventricular arrhythmias referred to all other VPB and 'all' ventricular arrhythmias included either 'significant' or 'non-significant' ventricular arrhythmias.

The incidence of ventricular arrhythmias was also assessed relative to the site and size of infarction. All anteroseptal and anterolateral infarcts were included in the anterior group and all inferior, inferolateral, and true posterior infarcts were included in the inferior/posterior group.

Patients were arbitrarily divided into two groups on the basis of the maximum height of enzyme rise. Those patients with a peak AST (aspartate aminotransferase) of greater than 200 IU/l (mean 347 ± 151 SD) were compared with those with a peak AST less than 200 IU/l (mean 112 ± 50 SD). Creatine kinase measurements were not available on a regular basis at the onset of the trial and were not measured. Patients included in the group with cardiac failure in CCU were those who had interstitial or alveolar pulmonary oedema on chest radiograph or those with persistent hypotension, oliguria, and poor peripheral circulation.

PATIENT POPULATION

Patients were randomly selected from those treated in the coronary care unit of the Alfred Hospital who had definite myocardial infarction diagnosed on the basis of a typical history of chest pain, serial enzyme rises greater than 50 per cent above normal levels, and an evolving electrocardiographic pattern, with loss of R wave amplitude or development of new pathological Q waves.

One hundred and eight patients were initially entered into the trial consisting of 92 men and 16 women, with an average age of 54·2 years (range 37 to 68 years). Fifty-two patients had anterior infarction, 53 had inferior infarction, and 3 had true posterior infarction. Thirty-four patients did not complete the 12 months of follow-up (Table 1). Because of tape malfunction or battery failure 40 of 386 electrocardiogram tapes (10%) failed to record and as this was not discovered till a later date these tapes could not be repeated. As a result analysis could be performed on 95 entry tapes, 76 tapes at 3 and 6 months, 72 tapes at 9 months, and 66 tapes at 12 months.

The first 90 patients were considered for a prospective double blind trial to assess the effect of practolol 200 mg twice daily on the incidence of ventricular arrhythmias after infarction (Federman *et al.*, 1976). Many of the patients were unwilling or unsuitable for this study and increasing reports of the side effects of practolol led to premature cessation of the trial. The results showed no significant reduction in the incidence of ventricular

Table 1 *Patient withdrawals before 1 year*

Patient unwilling to continue	18
Patient geographically unsuitable for regular review	7
Death	4
Miscellaneous	5
Total	34

arrhythmias in patients on practolol though salvos of ventricular premature beats were present for a lower percentage of the hours studied (Federman *et al.*, unpublished). Those patients in the practolol study have been included in this present study. Forty-three patients had practolol on at least one their of 3-monthly reviews. The other cardiac medications taken by patients during the study included digoxin (39 patients), quinidine (7 patients), procainamide (3 patients), and propranolol (2 patients). There was no significant difference in the incidence of ventricular arrhythmias in patients taking these medications and those who were not and, therefore, the results are not presented separately.

A control group of 21 normal subjects from the hospital staff or their relatives was studied with 24-hour Holter monitoring on one occasion while performing their normal activities. These subjects had no past history of cardiac disease and were on no medications at the time of study. They all had a normal 12 lead electrocardiogram apart from one which showed a left anterior hemiblock and one which showed one atrial premature beat. All had normal chest *x*-ray films, were normotensive, and had a normal physical examination. There were 4 women and 17 men, average age 49·9 years (range 40 to 66 years).

DATA RECORDING AND ANALYSIS

Holter electrocardiogram tape monitoring was successful for an average of 21·9 hours (range 7 to 24 hours) in the post-infarction group and 20·8 hours (range 11 to 24 hours) in the control group. Tapes were analysed using an Avionics Dynamic Electrocardioscanner, initially model 650 and later model 660. A modified lead V5 was used. Tapes were scanned at fast speed, with rate sampling at each hour. All arrhythmias were analysed at normal speed with samples recorded on a strip chart recorder at 25 mm/s. In cases with a high incidence of arrhythmias the total tape was played back on to a multichannel recorder at 3·3 mm/s, with rhythm disturbances being read manually.

Table 2 *Incidence of 'significant' ventricular arrhythmias (VA) averaged over first year after infarction*

Arrhythmia	*% of patient studies with VA*	*% hours studied with VA*
VPB > 1 in 10 normal beats	45	37
Multifocal VPB	39	26
Salvos (2 or 3 VPB)	26	14
Bigeminy/Trigeminy	14	23
R on T phenomenon	4	—
Ventricular tachycardia (> 4 VPB)	1	—
Total	54	40

VPB, ventricular premature beats.

In each study the number of hours during which arrhythmias occurred was documented and by relating this to the total number of hours recorded the percentage of studied hours showing arrhythmia was assessed.

Statistical analysis was performed using the χ^2 test with Yates correction for continuity and the unpaired Student's t test.

Results

INCIDENCE OF VENTRICULAR ARRHYTHMIAS IN PATIENTS AFTER MYOCARDIAL INFARCTION (Table 2, Figs 1 and 2)

The total incidence of 'all' ventricular arrhythmias and the incidence of 'significant' ventricular arrhythmias were high at entry and remained persistently high at each 3-month study during the first year (Fig. 1). 'All' ventricular arrhythmias occurred in 80 per cent of patients averaged over the first year and 'significant' ventricular arrhythmias in 54 per cent of patients. The incidence of these arrhythmias was slightly lower at entry than at subsequent periods of study being 77 per cent for 'all' ventricular arrhythmias and 42 per cent for 'significant' ventricular arrhythmias. This difference was not statistically significant. Seventy-seven patients had 3 or more successful tapes for analysis and of these 61 (79%) showed significant ventricular arrhythmias on at least 1 tape, 3 (4%) showed no

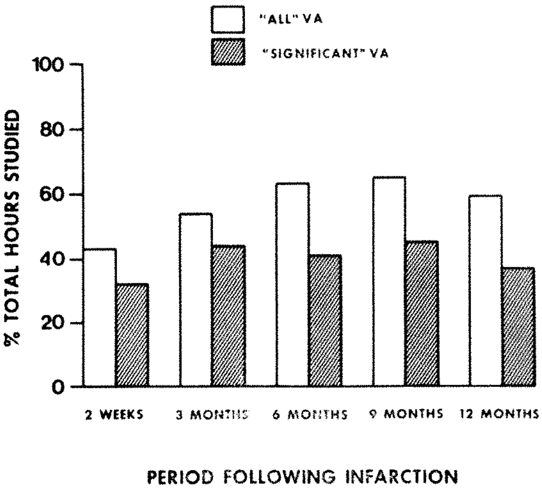


Fig. 1 *Incidence of 'all' and 'significant' ventricular arrhythmias (VA) at each study period in the first year after myocardial infarction.*

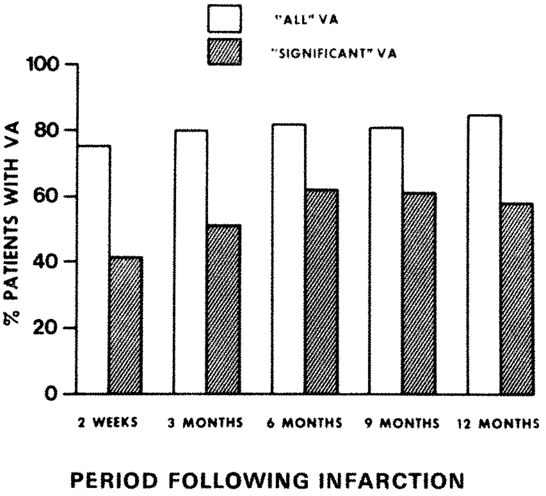


Fig. 2 *Percentage of studied hours that showed 'all' and 'significant' ventricular arrhythmias (VA) at each study period in the first year after myocardial infarction.*

ventricular arrhythmias on all studies, and 13 (17%) showed only non-significant ventricular arrhythmias.

'All' ventricular arrhythmias occurred for 57 per cent of the hours studied when averaged over the first year and 'significant' ventricular arrhythmias for 40 per cent of the hours studied. At entry the frequency of ventricular arrhythmias was significantly lower than for any of the other study periods being 43 per cent of the studied hours for 'all' ventricular arrhythmias (P < 0·0005) and 32 per cent of the studied hours for significant ventricular arrhythmias (P < 0·05).

The average incidence of the individual significant arrhythmias was high over the first year as was the percentage of studied hours for which they occurred (Table 2).

INCIDENCE OF VENTRICULAR ARRHYTHMIAS IN CONTROL PATIENTS

Of the 21 control patients, 10 (48%) had 'all' ventricular arrhythmias and 4 (19%) had 'significant' ventricular arrhythmias. These results were significantly lower than the corresponding results of 80 per cent and 54 per cent for the post-infarction patients, with P < 0·005 in both cases. 'All' ventricular arrhythmias occurred for 28 per cent of the hours studied in the control group with 'significant' ventricular arrhythmias occurring for 35 per cent of the hours studied. The result for 'all' ventricular arrhythmias was significantly lower than the 57 per cent of hours studied for post-infarction patients (P < 0·025); however, the difference did not reach significant levels for 'significant' ventricular arrhythmias.

When the individual 'significant' ventricular arrhythmias were analysed VPB > 1 in 10 occurred in 3 controls (14%) for 39 per cent of the hours studied, multifocal VPB in 2 controls (10%) for 24 per cent of the hours studied, and no controls had bigeminy/trigeminy, salvos, R on T phenomenon, or ventricular tachycardia. The incidence of VPB > 1 in 10 and multifocal VPB were both significantly lower than in the post-infarct group, with P < 0·025 in both cases.

INCIDENCE OF VENTRICULAR ARRHYTHMIAS RELATED TO INFARCT SITE

(Table 3, Figs 3 and 4)

At entry there was no significant difference in the incidence of ventricular arrhythmias between patients with inferior/posterior infarction compared with anterior infarction. After the entry study, however, the incidence for both 'all' and 'significant' ventricular arrhythmias was significantly higher in patients with inferior/posterior infarction as was the percentage of studied hours for which these arrhythmias occurred (Figs 3 and 4).

When the subsets of 'significant' ventricular

Table 3 *Incidence of 'significant' ventricular arrhythmias*

Arrhythmia	*Infarct site*		*Infarct size*		*Presence of failure in CCU*	
	Anterior	*Inferior/ Posterior*	*Peak AST < 200 IU/l*	*Peak AST > 200 IU/l*	*Absent*	*Present*
VPB > 1 in 10	39%	63%***	39%	54%***	44%	56%
Multifocal VPB	26%	54%***	28%	50%***	36%	54%**
Salvos	19%	35%	22%	30%	23%	38%*
Bigeminy/Trigeminy	10%	21%	13%	16%	15%	14%
R on T	1%	4%	2%	5%	4%	3%

P value *** < 0·0005
** < 0·005
* < 0·05

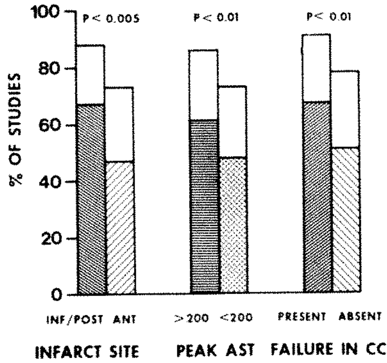
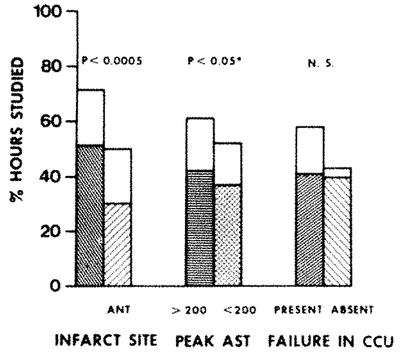


Fig. 3 *Incidence of ventricular arrhythmias (VA) averaged for all study periods related to infarct site, peak aspartate aminotransferase level (IU/l) and presence of cardiac failure while patient in the CCU. 'All' VA shown by height of column; 'significant' VA shown by shaded area.*

arrhythmias were analysed the higher incidence in inferior/posterior infarct patients after entry remained significant for each group except for R on T where the number of cases with this arrhythmia proved too small for significance to be reached (Table 3).

INCIDENCE OF VENTRICULAR ARRHYTHMIAS RELATED TO MAXIMUM ENZYME RISE
(Table 3, Figs 3 and 4)

In patients with a maximum AST greater than 200 IU/l there were 202 tape studies over the 12 months for analysis, compared with 184 tape studies in patients with a maximum AST less than 200 IU/l. Patients in the higher enzyme group proved to have a significantly greater incidence of ventricular arrhythmias over the first year after infarction (Fig. 3).



*FOR "ALL" VA ONLY
"SIGNIFICANT" VA N.S.

Fig. 4 *Percentage of studied hours that showed 'all' and 'significant' ventricular arrhythmias (VA) averaged for all study periods and related to infarct site, peak aspartate aminotransferase level (IU/l), and presence of cardiac failure while patient in CCU. 'All' VA shown by height of column; 'significant' VA shown by shaded area. *For 'all' VA only.*

The percentage of studied hours for which arrhythmias occurred was also higher in patients with a maximum AST greater than 200 IU/l, with this difference proving significant for 'all' ventricular arrhythmias ($P < 0{\cdot}05$) but not for 'significant' ventricular arrhythmias (Fig. 4).

When the individual subsets of 'significant' ventricular arrhythmias were analysed, patients with an AST greater than 200 had a significantly higher incidence of VPB > 1 in 10 and multifocal VPB. Though there was a higher incidence of bigeminy/trigeminy, salvos, and R on T phenomenon, these results were not statistically significant (Table 3).

INCIDENCE OF VENTRICULAR ARRHYTHMIAS RELATED TO PRESENCE OF CARDIAC FAILURE IN CORONARY CARE UNIT

In patients without failure in the CCU 299 studies were available for analysis compared with 87 studies for analysis in patients with cardiac failure in CCU. Patients with failure in CCU proved to have a significantly higher incidence of ventricular arrhythmias during the first year after infarction (Fig. 3). The percentage of studied hours for which arrhythmias occurred did not prove to be statistically different in the two groups.

When the individual significant arrhythmias were analysed there was a significant increase in the incidence of multifocal VPB ($P < 0{\cdot}05$) and salvos ($P < 0{\cdot}01$) in the group with failure in the CCU. The incidence of VPB > 1 in 10 was also higher in this group but did not reach significant levels and there was no increase in bigeminy/trigeminy.

RELATION OF HOLTER MONITORING TO RESTING ELECTROCARDIOGRAM

The results of Holter monitoring were analysed in patients who had a resting electrocardiogram showing no VPB at all periods of monitoring. These patients would normally have been considered to be free of VPB. In this group 231 tapes were analysed and 75 per cent showed 'all' ventricular arrhythmias for an average of 46 per cent of the hours studied and 43 per cent showed 'significant' ventricular arrhythmias for 30 per cent of the hours studied. These results though slightly lower than the overall incidence of ventricular arrhythmias observed in the post-infarction group were not significantly so. When the subsets of 'significant' ventricular

Table 4 *Deaths in first year*

Patient	*Infarct site*	*Holter monitoring result*	*Time and mode of death*
54 F	Inferior	Entry—non-significant VA for 24% hours studied	Died suddenly 2 months after infarct
61 M	Inferior	Entry—salvos in 1 hour; 3 months tape—no VA	Died suddenly 5 days after 3-month review
60 M	Anterior	Entry—non-significant VA for 21% hours studied	Inferior infarct 11 weeks after discharge; died after several cardiac arrests on 17th day
52 M	Anterior.	Entry—'non-significant' VA for 13% hours studied; 3 months tape—'non-significant' VA for 48% hours studied; 6 months tape—'all' VA for 95% hours studied, 'significant' VA for 86% hours studied	Died suddenly after chest pain 1 week after 6-month review

VA, ventricular arrhythmia.

arrhythmias were analysed 31 per cent of studies showed VPB > 1 in 10, 30 per cent showed multifocal VPB, 13 per cent showed bigeminy/trigeminy, 16 per cent showed salvos, 5 per cent showed R on T, and ventricular tachycardia was not observed.

In patients with 1 or more VPB on a resting electrocardiogram the corresponding Holter 24-hour tape monitor showed significant ventricular arrhythmias in 100 per cent of cases.

DEATHS (Table 4)
Four deaths occurred during the study period. All patients had ventricular arrhythmias on at least 1 occasion, and in the 3 patients dying suddenly 2 had shown 'significant' ventricular arrhythmias.

Discussion

The incidence of VPB is high at 2 weeks after myocardial infarction and remains persistently high during the first year. There is a tendency for VPB to become more frequent after the entry study at 2 weeks but this only became significant for the percentage of studied hours for which 'all' and 'significant' ventricular arrhythmias occurred (P values of < 0·0005 and < 0·05, respectively). A possible explanation is that the level of physical activity increases once patients leave hospital, and Jelinek and Lown (1974) have shown that the incidence of VPB may double during exercise with major repetitive VPB increasing by a factor approaching 8.

The total incidence of VPB in our series was 80 per cent which is similar to the incidence observed in other studies on patients with coronary artery disease. Lown *et al.* (1975) using 24-hour Holter monitoring found VPB to be present in 85 per cent of ambulatory patients, Moss *et al.* (1971) using 6-hour Holter monitoring found an incidence of VPB of 72 per cent at 3 weeks after infarction, and Kotler *et al.* (1973) found an incidence of 80 per cent using 12-hour Holter monitoring. The incidence of 'significant' ventricular arrhythmias was 54 per cent which is similar to the incidence of 41 per cent for 'advanced grade or repetitive forms' of VPB described by Lown *et al.* (1975) and the incidence of 42 per cent for 'serious' VPB described by Vismara *et al.* (1975b) in patients convalescing in hospital from acute myocardial infarction. The incidence of salvos (2 or 3 VPB) in our study was 26 per cent and ventricular tachycardia (> 3 VPB) was 1 per cent. Our incidence of ventricular tachycardia was lower than the 2·5 per cent observed by Kotler *et al.* (1973), the 4 per cent by Moss *et al.* (1971), and the 6 per cent by Vismara *et al.* (1975b), since in these studies ventricular tachycardia was defined as greater than 2 consecutive VPB.

Our control group, though small, had a lower incidence of 'all' and 'significant' ventricular arrhythmias (P < 0·005), with 'all' but not 'significant' ventricular arrhythmias occurring for a lower percentage of the hours studied (P < 0·025). Our incidence in this group of normal subjects was higher than the incidence described by Raftery and Cashman (1976) who used 24-hour Holter monitoring and found VPB in only 9 of 53 (17%) subjects who had previously been screened to exclude heart disease. Clarke *et al.* (1976), again in a screened population, found a higher incidence with 63 of 86 normal subjects (73%) having VPB. However only 10 of these (12%) showed VPB of 'serious prognostic significance'. Hinkle *et al.* (1969) studied a random group of 301 active men of median age 55 years who had not been screened. He found VPB in 62·2 per cent of subjects; however, there was a significant association between the presence of VPB and the presence of coronary heart disease at the time of examination. Patients with VPB had an increased risk of subsequent death from coronary heart disease. Thus, it appears that in patients with coronary artery disease the incidence of ventricular arrhythmias is higher than in the general population and that this may be the factor producing sudden death when the threshold to ventricular fibrillation is reduced during periods of ischaemia. All patients in our study who died suddenly had VPB on at least one of their studies and 2 of the 3 had shown 'significant' ventricular arrhythmias.

The Coronary Drug Project Research Group (1973) and the study by Chiang *et al.* (1969) have both shown an increased incidence of sudden death in patients with VPB present on a standard electrocardiogram. Our results and the results of others have shown a poor correlation between the incidence of VPB on a standard electrocardiogram and the incidence using Holter monitoring (Lown *et al.*, 1975). In patients with no VPB on their 12 lead electrocardiogram, 24-hour tape analysis showed that 75 per cent had 'all' ventricular arrhythmias and 43 per cent 'significant' ventricular arrhythmias. In those patients who had VPB on a 12 lead electrocardiogram the corresponding 24-hour Holter monitoring showed 'significant' ventricular arrhythmias in all cases. The 12 lead electrocardiogram is thus an insensitive method of assessing the presence of potentially serious arrhythmias; however, the presence of only 1 VPB on a standard electrocardiogram is likely to be associated with 'significant' ventricular arrhythmias on Holter monitoring.

During the convalescent period from infarction there is no difference in the incidence of ventricular arrhythmias for patients with inferior or true posterior infarction compared with anterior infarction. In the subsequent year, however, there is a significantly higher incidence of ventricular arrhythmias in patients with inferior/posterior infarction ($P < 0{\cdot}005$), with these arrhythmias occurring for a greater percentage of the studied hours ($P < 0{\cdot}0005$). Hinkle *et al.* (1969), Moss *et al.* (1971), Lown *et al.* (1975), and Vismara *et al.* (1975a, b) did not comment on the incidence of ventricular arrhythmias related to infarct site. However, Biddle *et al.* (1976) using 6-hour Holter monitoring have noted a higher incidence of 'serious ventricular arrhythmias' in patients with 'diaphragmatic' infarcts in the first 6 months after hospital discharge. The explanation for this finding is not clear though it may be related to the ability of patients with inferior infarction to return to a greater level of physical activity because of less left ventricular dysfunction.

In patients with evidence of more extensive myocardial damage as judged by a peak serum AST greater than 200 IU/l or with definite cardiac failure in CCU we found a greater incidence of ventricular arrhythmias during the first year after infarction ($P < 0{\cdot}05$). Biddle *et al.* (1976) noted that patients who had serious ventricular arrhythmias in the acute phase of infarction had significantly greater degrees of myocardial dysfunction as judged by pulmonary artery and pulmonary wedge pressures. In contrast to our results, however, they found no association between the long-term incidence of serious ventricular arrhythmias and the haemodynamic findings at the time of acute infarction.

The number of deaths during the first year of our trial have been small and no pattern of arrhythmias can be implicated as indicating a higher risk of sudden death since 79 per cent of patients who had 3 or more tapes showed significant ventricular arrhythmias on at least one occasion. There is obviously a need for long-term review and patients in the current series continue to be assessed 6-monthly and to have 24-hour Holter monitoring on a yearly basis. It is hoped that some pattern may be defined which will isolate those patients at increased risk. The recently reported Multicentre International Study (1975) and the study by Wilhelmsson *et al.* (1974) make a strong case for the use of long-term beta-adrenergic blocking agents to prevent sudden death; however, our experience with practolol showed no significant reduction in ventricular arrhythmias apart from a reduction in the percentage of studied hours for which salvos occurred (Federman *et al.*, 1976).

Conclusion

The incidence of ventricular arrhythmias is persistently high in the first year after myocardial infarction and is significantly higher than the incidence in normal control subjects. Patients with inferior/posterior infarction or those with evidence or more extensive myocardial damage have a higher incidence of ventricular arrhythmias in the long term.

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Immunological determination of serum m-AST activity in patients with acute myocardial infarction

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SUMMARY Serum m-AST (mitochondrial isoenzyme of AST) activity in patients with acute myocardial infarction was determined quantitatively by a new immunological technique which is sensitive and easily available. All 31 patients with acute myocardial infarction showed abnormally high levels of serum m-AST (more than 5 KU/ml); the mean serum m-AST activity attained its peak (42·0 ± 4·9 KU/ml) on the first day after the onset of infarction 5 hours later than that of serum t-AST (total AST) activity in 15 patients whose peak m- and t-AST activities were identified clearly. The individual peak m-AST activity correlated with the total CK released ($r = 0·83$, $n = 15$), indicating that the release of m-AST also reflects the infarct size. The ratio of serum m-AST/t-AST increased following myocardial infarction and showed the maximal value (average 25·7%) on the third to seventh day after onset. This ratio in the patients with acute myocardial infarction was also greater than that in patients with liver disease or with heart failure from causes other than acute myocardial infarction. In the patients who had the additional complication of heart failure and/or cardiogenic shock the ratio was also greater than that in the patients without these hazards. These results indicate that the ratio of serum m-AST/t-AST reflects the severity of the myocardial cellular damage in acute myocardial infarction.

Aspartate aminotransferase (L:aspartate:2-oxoglutarate aminotransferase, E.C.2.6.1.1.; AST) consists of two isoenzymes, one associated with the cytoplasmic fraction (s-AST) and the other with mitochondria (m-AST) (Fleisher *et al.*, 1960; Borst and Peeters, 1961; Boyd, 1961; Massarrat and Lang, 1965). Since AST is mainly contained in striated muscle, myocardium, and liver, its serum activity has been found to rise in diseases of these organs (Schmidt *et al.*, 1967; Farmer *et al.*, 1970; Idéo *et al.*, 1971). Though the ratio of serum m-AST activity to total serum AST (t-AST) activity has been reported to represent the severity of cellular damage in liver disease (Schmidt and Schmidt, 1961; Idéo *et al.*, 1972), the clinical significance in myocardial infarction of m-AST and the ratio m-AST/t-AST remains unsettled, probably because the previous methods for the determination of m-AST using electrophoresis or column chromatography were inadequate in sensitivity as well as quantitatively (Fleisher *et al.*, 1960; Boyd, 1961; Bodansky *et al.*, 1966; Idéo *et al.*, 1971).

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Modern medical treatment of acute myocardial infarction, however, attempts to salvage the jeopardised myocardium surrounding the fully infarcted area. Thus, the evaluation of the degree of the cellular damage within the ischaemic myocardium and the assessment of the extent of infarcted area are of great importance.

Recently Wada *et al.* (1976) described a new immunological technique for the determination of serum m-AST activity which is more sensitive and more easily available than previous methods. Accordingly, in the present study we used this new method to investigate the serial changes of serum m-AST activities and also the ratio of the serum m-AST/t-AST in patients with acute myocardial infarction. The results were compared with those in patients with liver disease and with cardiac failure as well as with normal controls.

Subjects

NORMAL SUBJECTS

Eighty-two healthy subjects (42 men and 40 women, whose ages ranged from 20 to 71 years, average 42 years) were studied to determine the normal range of serum m-AST activity. In order to match the age range of a control group with that of the patients with acute myocardial infarction, 27 subjects of more than 50 years were also selected; the average age was 56·3 years.

ACUTE MYOCARDIAL INFARCTION

Serum m-AST, t-AST, and creatine kinase (CK) activities were determined in 31 patients with acute myocardial infarction whose onset of infarction was clearly identified. There were 26 men and 5 women, whose ages ranged from 35 to 76 years (average 61·5 years). None of these patients died within a week of onset of the illness. The diagnosis of myocardial infarction was established by a history of typical chest pain, characteristic electrocardiographic abnormalities, and an increase in serum enzyme activities (CK, lactic dehydrogenase, and α-hydroxybutyric dehydrogenase).

In all patients we measured (i) the individual peak levels of serum m-AST and t-AST, (ii) the interval from the onset of symptoms to the peak levels of serum m-AST and t-AST activities, and (iii) the serial changes in the ratio m-AST/t-AST. The total CK released, which represents the infarct size, was also obtained by the method of Sobel *et al.* (1972) modified by Norris *et al.* (1975) in 15 patients without cardiogenic shock or severe arrhythmia in the acute phase who survived for more than 7 days.

In order to investigate the relation between serum m-AST levels and the complication of pump failure, the 31 patients were divided into two groups according to the criteria of Killip and Kimball (1968): group 1 consisted of 19 patients (average age 57·6 years) without heart failure, and group 2 of 12 patients (average age 67·2 years) with heart failure and/or cardiogenic shock.

CARDIAC FAILURE

In order to investigate the contribution of the m-AST released from liver in the patients with heart failure but without muscular necrosis, serum m-AST and t-AST activities were determined in 16 patients (average age 44·5 years) with cardiac failure caused by valvular disease (11 patients) or congestive cardiomyopathy (5 patients).

LIVER DISEASE

The ratio of m-AST/t-AST in 23 patients with acute or chronic hepatitis, not including fulminant hepatitis (average age 40·3 years), and 12 patients with liver cirrhosis (average age 53·3 years) were compared with the ratios in patients with acute myocardial infarction.

Methods

A new method for the determination of serum m-AST activity is based on the difference in the immunological properties of the isoenzymes. Serum m-AST activity was assessed as the total residual AST activity after complete removal of s-AST (cytoplasmic fraction) with the immunoadsorbent, red blood cells sensitised with anti-s-AST antibody.

(i) PREPARATION OF IMMUNOADSORBENT

Anti-s-AST antibodies were prepared in rabbits by injecting the purified human s-AST with Freund's complete adjuvant. Purification of s-AST was performed by the method of Morino *et al.* (1963). The IgG fraction was purified by the modified method of Petersen *et al.* (1961) from the anti-sera; its anti-s-AST titre is higher than 1:10 000. IgG fraction was mixed with 2 volumes of phosphate buffer solution containing 50 per cent sheep red cells. One volume of 5 per cent glutaraldehyde solution was added to this mixture with stirring. Red cells precipitated centrifugation were thoroughly washed with phosphate buffer solution and suspended in phosphate buffer solution so as to give a concentration of 20 per cent. This suspension was used as the immuno-adsorbent of s-AST.

(ii) ASSAY OF m-AST ACTIVITY

To determine the serum m-AST activity, s-AST was removed from the test serum with the immunoadsorbent described above. The immunoadsorbent (1 ml) was suspended in 5 ml of 0·15 M phosphate buffer solution (pH 7·2). The mixture was centrifuged at 1500 *g* for 3 minutes and the precipitate was mixed thoroughly with 0·5 ml of the serum specimen. The mixture was allowed to stand at room temperature for about 5 minutes, with occasional stirring. The immunoadsorbent was completely removed by centrifugation at 1500 *g* for 5 minutes and 0·2 mg/ml of the supernatant solution was used to assay the m-AST activity. M-AST and t-AST activity was measured by the spectrophotometric method coupled with malic dehydrogenase and expressed in Karmen units.

(iii) RELIABILITY OF METHOD

In order to evaluate the reliability of this method we prepared the standard AST sera containing known amounts of m- and s-AST with various ratios of these isoenzymes (see Table 1). The standard sera were prepared from crystallised m- and s-AST obtained from the pig heart by the method of Morino *et al.* (1977); the respective activities of these isoenzymes can be determined by the spectrophotometric technique as described above. Measure-

Table 1 *Test of accuracy of m-AST determination by immunoadsorbent method. Standard sera were prepared from crystallised m-AST and s-AST of pig heart*

AST standard serum						
	s-AST	200	200	200	200	200
	m-AST	10	20	40	80	160
Measured activity of m-AST		9	22	40	82	163

Activity is expressed in KU/ml.

ment of m-AST activity of these standard sera by our new method revealed the excellent reliability of the method and the electrophoresis of the serum from which the s-AST is removed with immunoadsorbent showed only a band which was completely identical with a band produced by crystallised m-AST, indicating that s-AST activity can be assessed as the difference between the activities of t- and m-AST for routine work (Table 1).

Results

(1) NORMAL VALUE OF SERUM m-AST ACTIVITY

The mean serum m-AST activity determined in 82 healthy subjects was 1·0 KU/ml, ranging from 0 to 6 KU/ml. The mean value of serum m-AST in 17 patients more than 50 years old was 1·5 KU/ml (0 to 5 KU/ml).

To evaluate the reproducibility of our method, we determined in triplicate the m-AST activity of each of 15 serum samples from patients with myocardial infarction. The maximum error in determination was 8·4 per cent (mean error was 6·4%), indicating a good reproducibility of the method.

(2) SERUM m-AST ACTIVITY IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

(i) *Serial changes of serum m-AST activities*

Fig. 1 shows the serial changes of the mean serum m-AST activities in 31 patients with acute myocardial infarction. On the day of onset the mean m-AST activity was raised (20·2 ± 2·9 KU/ml) and increased to the maximum (42·0 ± 4·9 KU/ml) on the first day after infarction, decreasing gradually thereafter to the normal level (< 5 KU/ml) on the ninth day of infarction. When more than two determinations were performed in a day, a value obtained early in the morning was illustrated as a representative value of an individual for that day after onset. The mean t-AST activity also showed a peak value (280·5 ± 38·2 KU/ml) on the first day after onset of infarction (see Fig. 2) but returned to normal on the seventh day after onset. In 15 patients whose serum m-AST and t-AST activities were determined every 4 hours within the first 24 hours and thereafter every 6 hours until CK activity returned to normal, the mean peak m-AST activity (65·7 ± 9·8 KU/ml) was obtained on average at 34·6 ± 3·2 hours after the onset of infarction, returning to

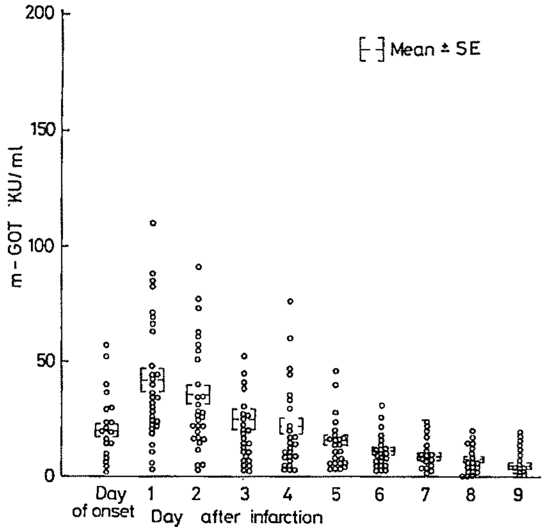

Fig. 1 *Daily serum m-AST activities in 31 patients with acute myocardial infarction.*

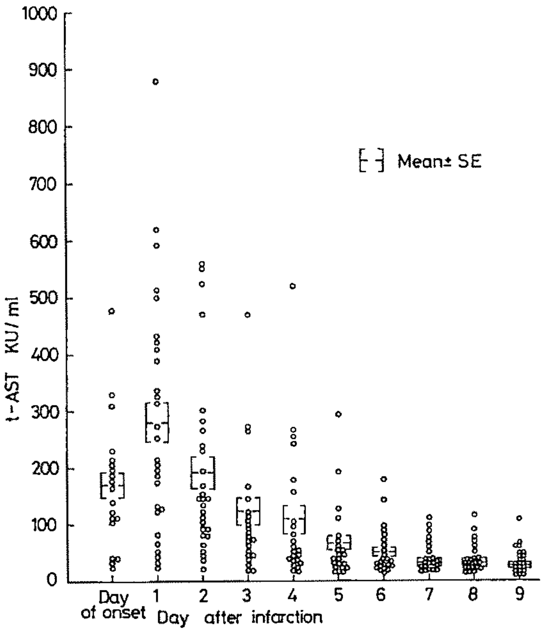

Fig. 2 *Daily serum t-AST activities in 31 patients with acute myocardial infarction.*

Table 2 *Ratio m-AST/t-AST after onset of infarction in groups 1 (without heart failure) and 2 (with heart failure and/or cardiogenic shock (mean ± SE (%))*

		Day after onset								
	Day of onset	*1st*	*2nd*	*3rd*	*4th*	*5th*	*6th*	*7th*	*8th*	*9th*
Group 1	14·5 ± 2·1	17·5 ± 2·0	17·6 ± 2·1	21·3 ± 2·2	21·8 ± 2·1	23·6 ± 2·2	25·3 ± 2·0	26·4 ± 2·2	19·0 ± 4·1	20·5 ± 2·6
				*						
Group 2	20·3 ± 4·4	16·5 ± 3·0	20·3 ± 4·0	33·6 ± 5·1	26·3 ± 3·7	25·4 ± 4·0	23·1 ± 1·5	23·0 ± 4·5	24·4 ± 6·0	32·5 ± 10·5
Total	16·8 ± 2·1	17·1 ± 1·6	18·0 ± 1·7	25·7 ± 2·5	23·7 ± 2·0	23·8 ± 1·9	24·6 ± 1·4	24·3 ± 2·9	21·5 ± 3·3	23·1 ± 3·4

* P < 0·01.

normal on the ninth day after the onset, while the mean peak t-AST was 420·7 ± 50·5 KU/ml which was obtained on average 29·4 ± 2·9 hours after the onset (about 5 hours earlier than that of m-AST), returned to normal on the seventh day of infarction.

The mean ratio of the individual serum m-AST to t-AST activity (m-AST/t-AST) increased gradually after infarction reaching a maximum (25·7 ± 2·5%) on the third day after onset (Table 2). Though individual values of this ratio showed a wide range at each study interval, the mean of the ratios m-AST/t-AST in 12 patients in group 2 (with heart failure and/or cardiogenic shock) was higher than that in 19 patients in group 1 (without heart failure) at every study interval except the first, sixth, and seventh day after onset (see Table 2). On the third day after infarction the maximal mean m-AST/t-AST was obtained. This ratio in group 2 was 33·6 ± 5·1 per cent which was significantly greater than that in group 1 (21·3 ± 2·2%, P < 0·01).

(ii) *Relation between peak value of serum m-AST activity and total CK released*

In 15 out of 31 patients serum m-AST and CK activities were determined every 4 hours within the first 24 hours and thereafter every 6 hours until CK activity returned to normal, and the relation between the peak serum m-AST activity and the total CK released (which directly reflects infarct size) was investigated. The individual peak m-AST activities (Fig. 3) showed a close correlation with the total CK released (r = 0·83, n = 15), indicating that the peak m-AST activity also reflects infarct size.

(3) SERUM m-AST ACTIVITY IN PATIENTS WITH HEART FAILURE

The average serum m-AST and t-AST activities were 19·3 ± 6·0 (3-102) KU/ml, and 164·1 ± 51·0 (37-830) KU/ml, respectively, in 16 patients with heart failure caused by valvular heart disease or congestive cardiomyopathy but without infarction. The ratio m-AST/t-AST averaged 12·2 ± 1·0 per cent (6·0 -21·7%) which was substantially less than that of the patients with acute myocardial infarction —statistically significant from the third to seventh day after onset (P < 0·01).

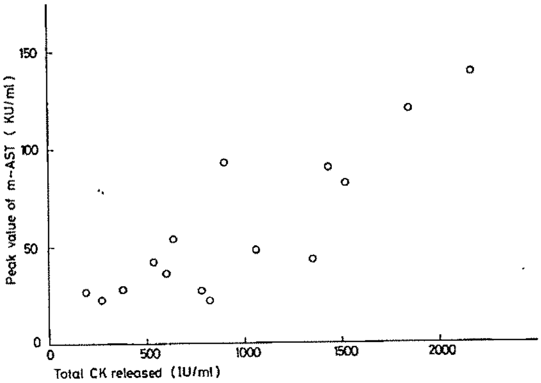

Fig. 3 *Relation between the peak m-AST activity and the total CK released.*

(4) SERUM m-AST ACTIVITY IN PATIENTS WITH LIVER DISEASE

The mean serum m-AST activity was 8·9 ± 2·0 (0-70) KU/ml in 23 patients with acute or chronic hepatitis, while the mean serum t-AST activity was 70·5 ± 11·3 (11-246) KU/ml. In 12 patients with liver cirrhosis the mean m-AST activity (17·3 ± 5·4 KU/ml) was slightly greater than that of the patients with hepatitis.

The mean values of the ratios m-AST/t-AST in the patients with hepatitis and liver cirrhosis were 12·7 ± 1·8 per cent and 11·3 ± 2·0 per cent, respectively, both being significantly less than the values obtained from third to seventh day after onset in acute myocardial infarction (P < 0·01).

Discussion

In 1961 Borst and Peeters (1961) reported that aspartate transaminase has two isoenzymes corresponding to cytoplasmic and mitochondrial fractions (s-AST and m-AST). In patients with liver disease, the detection of serum m-AST activity has been considered to reflect severe cellular damage (Schmidt and Schmidt, 1963). The clinical significance of serum m-AST activity in acute myocardial infarction, however, was unknown. This is partly because the previous methods using electrophoresis or column chromatography allow only semiquantitative determination with inadequate sensitivity.

In the present study we assessed serum m-AST activities quantitatively in patients with acute myocardial infarction by an immunological method with high sensitivity which was recently reported by Wada and his associates (1976). All patients in our series showed abnormal high m-AST activity (18 to 132 KU/ml). Their peak values correlated with the total CK released, which has been shown to be related to infarct size (Sobel *et al.*, 1972; Inoue *et al.*, 1977). This finding strongly suggests that in patients with acute myocardial infarction m-AST activity is derived from the myocardium and hepatic m-AST contributes only minimally to serum m-AST activity. Myocardial and hepatic m-AST are immunochemically identical (Morino *et al.*, 1964).

Our results also showed that the peak values of m-AST were obtained on the average 5 hours after the peak of t-AST activity. These results agree with the report by Murros *et al.* (1973) that serum m-AST activity determined by electrophoresis increased to above normal in 23 of 24 patients with acute myocardial infarction and that its peak level was usually obtained later than that of t-AST, indicating the delayed release of m-AST into the circulation.

Although Calva *et al.* (1974) also described this delay in the peak time of m-AST activity in coronary occlusion in 5 of 10 dogs, they could not detect serum m-AST activity in two infarcted dogs. In contrast to this and other previous reports (Fleisher and Wakim, 1961; Bodansky *et al.*, 1966; Murros *et al.*, 1973), all the patients with acute myocardial infarction in our study had abnormally high m-AST activities. This difference suggests that our immunological method, using the sensitised erythrocytes of sheep to eliminate the antigen-antibody complex of s-AST, has higher sensitivity than the previous technique. Indeed we detected serum m-AST activity in 31 of 35 patients with liver disease, though Murros *et al.* (1973) could not detect m-AST activity in the serum of their patients with liver disease whose serum t-AST was less than 100 KU/ml, even with the immunological technique.

The improvement in sensitivity for determination of m-AST activity, however, could result in a higher value for the ratio m-AST/t-AST. In our study the mean value of the individual maximal m-AST/t-AST was 30·2 ± 1·7 per cent (12 to 64) and this value is significantly greater than those in the patients with liver disease previously reported (Farmer *et al.*, 1970; Idéo *et al.*, 1971). In the present study, the mean ratio of m-AST/t-AST in 35 patients with liver disease was 12·2 ± 1·9 per cent and was similar to the previous reported results (Fleisher and Wakim, 1961). Accordingly our results strongly suggest that the ratio of m-AST/t-AST in acute myocardial infarction is larger than it is in liver disease and confirm the work of Farmer *et al.* (1970).

There are two possible reasons for this difference in the ratio m-AST/t-AST between acute myocardial infarction and liver disease. The first possibility is that the ratio m-AST/t-AST of the myocardial tissue is greater than that of liver, and this difference is reflected in the larger ratio of serum m-AST/t-AST in patients with acute myocardial infarction. Bodansky *et al.* (1966) reported that the ratios of m-AST/t-AST in myocardial tissue and in liver tissue were 68 and 49 per cent, respectively. Recently, however, one of the authors (H.W.) also determined these ratios in the myocardium and liver by our method, and showed that the liver contained a higher percentage of m-AST (71·0%) than the myocardium (64·0%, unpublished data). This finding made it difficult for us to accept the first possibility that the higher ratio m-AST/t-AST in myocardial infarction was the result of the higher content ratio of the myocardium.

The second possibility is that the larger ratio of serum m-AST/t-AST reflects severe cellular insult to the mitochondria. Calva *et al.* (1974) reported that higher levels of m-AST were observed when the necrosis was extensive and transmural, and in dogs with extensive infarction the ratio of serum m-AST/t-AST was more than 25 per cent. In our cases also the serum m-AST/t-AST was smaller in group 1 (without heart failure). This result was incompatible with the study of Calva *et al.* (1974) which showed the mean total CK released was significantly greater in group 2 than in group 1. These results strongly suggest that the serum m-AST/t-AST reflects the degree of the myocardial tissue damage in acute myocardial infarction. The reduction of the ratio of serum m-AST/t-AST (the mean maximal ratio; 30·2%) from that of myocardial m-AST/t-AST (64·0%) might be the result of the higher lability of m-AST than s-AST (cytoplasmic AST) as suggested by the previous studies of Fleisher and Wakim (1961).

However, the substantially large ratio of m-AST/t-AST was obtained on the third to seventh day after onset, a few days after the peak of m-AST, which indicates that there is a gradual release of m-AST from the damaged myocardium several days after infarction since the disappearance rate of m-AST in serum was reported to be more rapid than that of s-AST (Fleisher and Wakim, 1961). Though our results indicate that the m-AST/t-AST could be an index of severity of infarction, further investigations are needed to elucidate the quantitative relation between the release of m-AST and the degree of myocardial damage.

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Determination of right ventricular wall thickness in systole and diastole

Echocardiographic and necropsy correlation in 32 patients

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SUMMARY To show that right ventricular wall thickness (RVWT) measurements can be made with precision by echocardiography, we correlated these measurements with those obtained at necropsy in 32 terminal patients. The correlation between the echocardiographic diastolic right ventricular wall thickness (mean 4·0 ± 1·62 mm) and the necropsy measurement (mean 4·3 ± 1·52 mm) was good ($r = 0{\cdot}83$) in all 32 patients with normal or increased right ventricular wall thickness at necropsy. In 19 patients without necropsy evidence of right ventricular hypertrophy (RVWT $\leqslant$ 4 mm), the mean diastolic and systolic right ventricular wall thicknesses were 3·0 ± 0·92 mm and 5·1 ± 1·64 mm, respectively. In 13 patients with necropsy evidence of right ventricular hypertrophy (RVWT $\geqslant$ 5 mm), the mean diastolic and systolic right ventricular wall thicknesses were 5·3 ± 1·56 mm and 8·2 ± 1·88 mm, respectively. We conclude that technically satisfactory echocardiograms of the right ventricular wall can be obtained in adults and that these allow measurement of systolic and diastolic right ventricular wall thicknesses. Echocardiography can reliably estimate the diastolic wall thickness and may be helpful in the evaluation of right ventricular hypertrophy.

Visualisation of the wall of the right ventricle is difficult in man. The right ventricular free wall is not traceable from cine-angiocardiograms (Arcilla *et al.*, 1976), and can only be measured at necropsy (Sokolow and Lyon, 1949; Allenstein and Mori, 1960; Selzer *et al.*, 1960; Flowers and Horan, 1972). The right ventricular cavity dimension can be estimated by echocardiography by measuring from an assumed location of the anterior border of the right ventricle 5 mm from the chest wall echoes (Popp *et al.*, 1969; Feigenbaum, 1976) to the right side of the interventricular septum.

Recently, right ventricular wall thickness has been measured in children by echocardiography (Hagan *et al.*, 1973; Solinger *et al.*, 1973; Epstein *et al.*, 1975; Goldberg *et al.*, 1975). These echocardiographic measurements have not been validated with necropsy findings, though the diastolic measurements correlate well with the wall thickness measured using callipers at the time of open heart surgery (Arcilla *et al.*, 1976). Right ventricular wall thickness and motion have not been evaluated in adults and no measurements are available (Joyner, 1974; Gramiak and Waag, 1975; Chang, 1976; Feigenbaum, 1976). To show that measurements of right ventricular wall thickness can be made with precision in adults by echocardiography we correlated these measurements with those obtained at necropsy in 32 male patients. This paper reports the results of this study.

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Subjects and methods

All terminal patients known to us were studied by echocardiography. Thirty-two of these patients died within one month of echocardiography and necropsy measurements of right ventricular wall thickness were made (Table).

ECHOCARDIOGRAPHIC TECHNIQUE FOR OBTAINING RIGHT VENTRICULAR WALL ECHOES

The echocardiographic recordings were made using a strip chart recorder with the patient in the supine position. A 2·25 MHz transducer was used to record the right ventricular wall echoes in all patients. As the chest wall gives strong echoes, this can result in poor resolution of the anterior right ventricular

Table *Correlation of echocardiographic and necropsy measurements of right ventricular wall thickness in all patients*

Patient number	*Age (y)*	*Diagnosis*	*Necropsy (mm)*	*Echocardiogram (mm)*	
				diastole	*systole*
1	56	Coronary heart disease	6	6	10
2	71	Coronary heart disease	7	6	10
3	59	Cardiomyopathy	6	5	7
4	63	Coronary heart disease	6	5	7
5	87	Cardiomyopathy	6	7	9
6	57	Coronary heart disease	5	6	9
7	38	Coronary heart disease	5	5	8
8	39	Coronary heart disease	5	5	8
9	48	Coronary heart disease	5	5	7
10	78	Coronary heart disease	3·5	4	6
11	54	Coronary heart disease	3	2	5
12	76	Coronary heart disease	3	3	4
13	55	Coronary heart disease	3	3	4
14	59	Coronary heart disease	2	2	3
15	61	Cardiomyopathy	4	3	5
16	56	Cardiomyopathy	3	3	4
17	84	Coronary heart disease	3	4	8
18	62	Cardiomyopathy	3	3	5
19	60	Coronary heart disease	4	2	5
20	66	Coronary heart disease	4	2	5
21	56	Coronary heart disease	3	2	6
22	62	Coronary heart disease	3	3	5
23	45	Coronary heart disease	3	3	5
24	56	Coronary heart disease	3	2	2
25	50	Cardiomyopathy	4	2	5
26	64	Cardiomyopathy	7	6	10
27	48	Coronary heart disease	6	5	9
28	60	Cardiomyopathy	6	6	10
29	56	Coronary heart disease	6	6	10
30	81	Coronary heart disease	4	5	9
31	54	Coronary heart disease	3	3	5
32	40	Cardiomyopathy	4	4	6

wall. It was necessary to adjust carefully the coarse gain, near gain, and depth compensation controls to record right ventricular wall echoes adequate for measurement of wall thickness. Placement of the depth compensation ramp and its angle of slope are not fixed for recording the right ventricular wall. This control is used to suppress echoes close to the transducer and to increase the intensity of echoes farther away from the transducer. The depth compensation settings recommended for echocardiographic examination of the left ventricle (Chang, 1976) are not appropriate for obtaining echograms of the right ventricular wall.

In our experience, right ventricular wall echoes were clearly seen only when we specifically looked for them. On a routine echocardiogram for a left ventricular study, the right ventricular wall was not well defined (Fig. 1A, left panel). On reducing the near gain, the right ventricular wall echoes were better seen (Fig. 1A, right panel). In the last two beats the right ventricular wall echoes are reasonably clear, though the right ventricular wall could not be completely separated from the chest wall. In Fig. 1B, separation of right ventricular wall from the chest wall was achieved by decreasing the near gain and increasing the coarse gain. Though the right ventricular wall is well seen in both panels of Fig. 1B, the left panel is better suited for assessing the right ventricular wall thickness and motion than the right panel, as it has higher gain and darker colour. The right ventricular wall shows a posterior motion away from the chest wall during systole, and is thicker in systole than in diastole (Figs 2 and 3). The anterior echo-free space seen in Fig. 1B is not the result of the pericardial effusion. No posterior echo-free space was present in any patient though we specifically looked for pericardial effusion by standard techniques (Horowitz *et al.*, 1974). The right ventricular wall thickness was measured from the pericardium to the endocardial surface of the right ventricle at a level where the interventricular septum, mitral valve, and posterior left ventricular wall were well seen; end-diastolic measurements were made at the beginning of QRS, and systolic measurements when right ventricular wall thickness was greatest.

NECROPSY TECHNIQUES

At necropsy the hearts were dissected in a uniform manner and the right ventricular wall thickness measurements were made without knowledge of the echocardiographic measurements. The right ventricular wall thickness was measured in millimetres with a ruler, in the mid-portion of the free wall of the right ventricle (between the base and the apex). Sections were carefully made to avoid the valleys between the trabeculations. The normal right ventricular wall thickness at necropsy is 2 mm, and right ventricular hypertrophy is usually considered to be present if the wall thickness is 5 mm or more.

Results

The diastolic and systolic measurements of right ventricular wall thickness were correlated with the necropsy measurements. The correlation between diastolic wall thickness measured by echocardiography (mean 4·0 ± 1·62 mm) and at necropsy (4·3 ± 1·52 mm) was good (r = 0·83) in all 32 patients (Fig. 4). The correlation between the systolic wall thickness measured by echocardiography (6·4 ± 2·42 mm) and at necropsy was less good (r = 0·59).

There were 19 patients without right ventricular hypertrophy, having a wall thickness 4 mm or less at necropsy. The mean diastolic right ventricular wall thickness measured at echocardiography was 3·0 ± 0·92 mm (range 2-5 mm) and the mean systolic measurement was 5·1 ± 1·64 mm (range 2-9 mm).

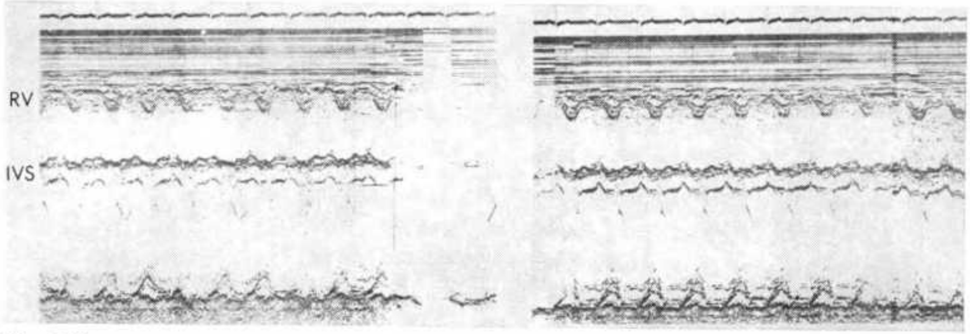

Fig. 1(A)

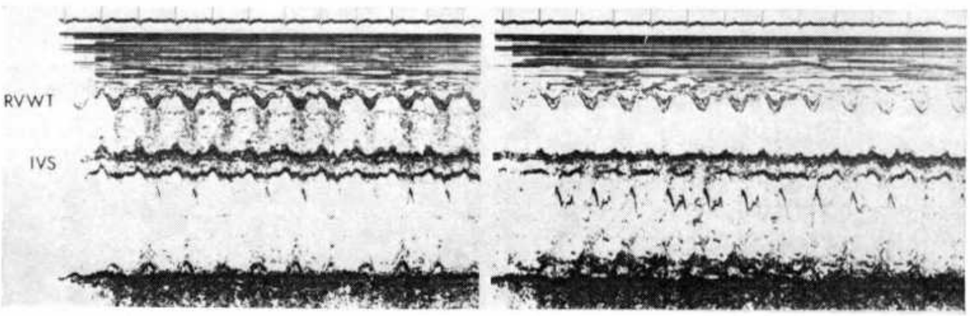

Fig. 1(B)

Fig. 1(A) *(left panel) Right ventricular (RV) wall seen on a routine study is not separate from the chest wall echoes. This is because of a high near gain. On the right side of left panel the gain is decreased abruptly with the right ventricular wall almost disappearing. (right panel) The right ventricular wall is seen better. The endocardial margins are more distinct, but the right ventricular wall and chest wall echoes are still close to each other. Though this echo is not optimal for right ventricular wall thickness measurement, the right ventricular dimension can be accurately measured from the endocardium of the right ventricular wall to the right side of septum. Thus, one would not have to use the customary approximation of about 0·5 cm from the chest wall echoes as to the location of the anterior border of the right ventricle. The last two beats of the tracing show a clear right ventricular wall.* (B) *An optimal right ventricular wall recording from the same patient. The chest wall echoes have been suppressed by manipulation of the near gain, coarse gain, and the depth compensation controls. The right ventricular wall is separated from the chest wall by an anterior echo-free space not caused by a pericardial effusion. The thickness and motion of the right ventricular wall can be evaluated from this echocardiogram. During systole the right ventricular wall thickens and moves away from the chest wall in a posterior direction. The right panel shows a reduction in gain with virtual disappearance of the right ventricular wall echoes in the last few beats.*

There were 13 patients with right ventricular hypertrophy as evidenced by right ventricular wall thickness 5 mm or more at necropsy. The mean diastolic wall thickness measurement by echocardiography was 5·3 ± 1·56 mm (range 5-6 mm) and the mean systolic thickness measurement was 8·2 ± 1·88 mm (range 6-10 mm).

Discussion

Our data show that echocardiographic measurements of diastolic right ventricular wall thickness correlate well ($r = 0{\cdot}83$) with necropsy measurements. This is supported by the study of Arcilla *et al.* (1976) where good correlation ($r = 0{\cdot}87$) was found in 15 children between right ventricular wall thickness measured with callipers at the time of open heart surgery and that obtained by echocardiography. In our study the mean diastolic wall thickness was 3·0 mm in patients without right ventricular hypertrophy, and was 5·3 mm in patients with necropsy evidence of right ventricular hypertrophy. Similarly, the mean systolic right ventricular wall thickness was 5·1 mm in patients without right ventricular

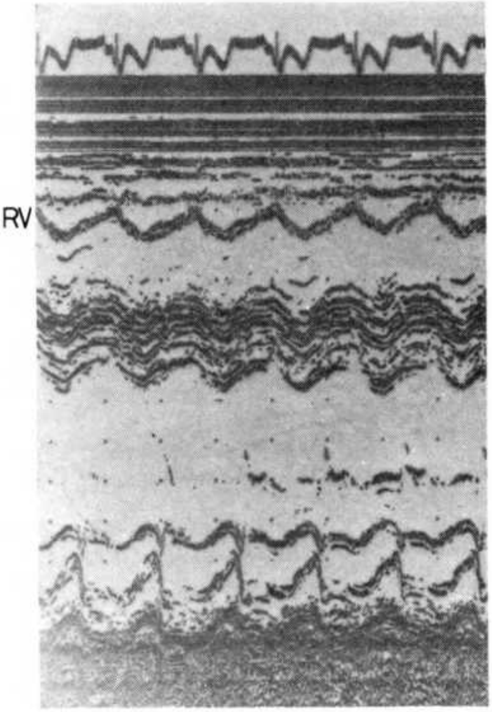

Fig. 2 *The echocardiogram from a patient with a thin right ventricular (RV) wall. This is completely separated from the chest wall by decreasing the near gain and increasing the coarse gain. To ensure that the right ventricular wall thickness was seen in full, the gain was increased until the endocardial border was complete. The right ventricular wall does not thicken in systole, but has very good motion. The anterior echo-free space is not the result of a pericardial effusion.*

hypertrophy, and was 8·2 mm in patients with necropsy evidence of right ventricular hypertrophy. These measurements of right ventricular wall thickness in adults may be helpful in evaluating right ventricular hypertrophy and right ventricular mass (Arcilla *et al.*, 1976).

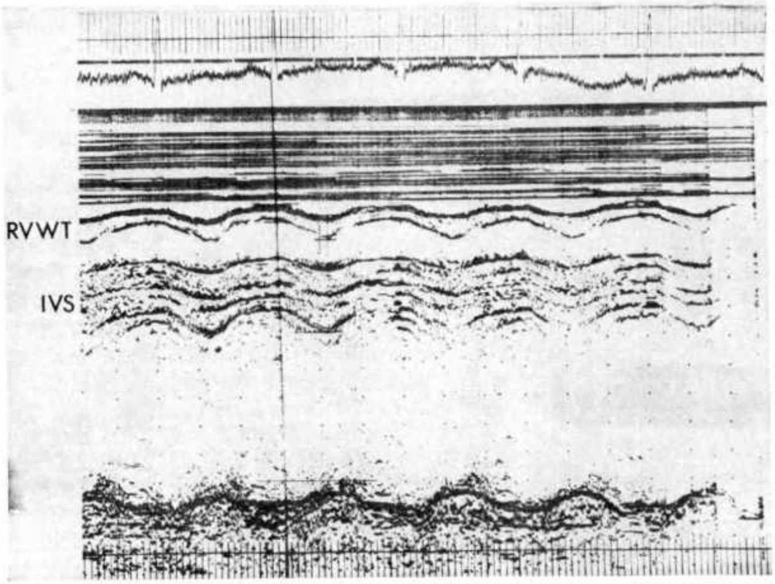

Fig. 3 *A distinct right ventricular wall completely separated from the chest wall by an echo-free space (not due to pericardial effusion) is shown here. Both margins of the right ventricular wall are distinct, and the diastolic and systolic measurements of its thickness can be accurately made. The right ventricular wall thickens during systole, has good motion, and displays a posterior motion away from the chest wall.*

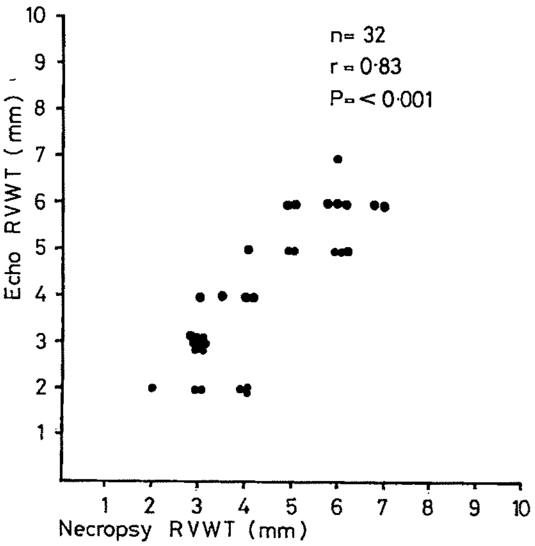

Fig. 4 *Correlation between the echocardiographic measurements of right ventricular wall thickness (RVWT) and the necropsy measurements was good (r = 0·83) in 32 patients. The diastolic RVWT for all patients ranged between 2 and 6 mm (mean 4·0 ± 1·62 mm), the systolic RVWT ranged between 2 and 10 mm (mean 6·4 ± 2·42 mm), and the necropsy RVWT ranged between 2 and 7 mm (mean 4·3 ± 1·52 mm).*

It has been said that the anterior right ventricular wall is difficult to record in the absence of significant anterior pericardial effusion and is clearer in the presence of exaggerated motion, as seen in hypertrophic subaortic stenosis (Feigenbaum, 1976). In our study, the recording of clear right ventricular wall echoes was unrelated to the magnitude of right ventricular wall excursion. Furthermore an anterior echo-free space could be seen in the absence of pericardial effusion, as has been described before (Solinger *et al.*, 1973; Horowitz *et al.*, 1974; Epstein *et al.*, 1975). Our success in obtaining satisfactory right ventricular wall echoes is in large part the result of our interest in measuring wall thickness and not because of new technical advances. Good quality echograms appropriate for right ventricular wall thickness measurement were obtained in nearly 90 per cent of subjects up to 18 years of age by Arcilla *et al.* (1976), and in 73 of 77 children by Allen *et al.* (1977).

We conclude that technically satisfactory echocardiograms of the right ventricular wall can be obtained in men which allow measurements of systolic and diastolic wall thickness. Measurements of diastolic right ventricular wall thickness by echocardiography correlate well with necropsy measurements, and may be useful in the non-invasive evaluation of right ventricular hypertrophy and mass in man.

We thank Dr Paul Lindsay and Miss Becky Brotton for help with this study.

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Noninvasive assessment of left ventricular function in myotonic muscular dystrophy

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SUMMARY In order to assess left ventricular function, measurements of left ventricular internal dimension and its rate of change have been made by echocardiography in 7 patients with myotonic dystrophy and the three children of one of them, who were clinically normal but had abnormal muscle biopsies. Electrocardiograms and systolic time intervals were also recorded in all. Only one patient had signs of overt heart disease and an abnormal electrocardiogram (type B WPW). Systolic time intervals were normal in all 7 patients. Five subjects had echocardiographic abnormalities, which were of minor degree except in the patient with overt heart disease who had considerable impairment of both systolic and diastolic left ventricular function. Another patient had abnormalities of both systolic and diastolic function; systolic abnormalities occurred alone in one patient and diastolic abnormalities alone in one relative.

It is concluded that patients with myotonic dystrophy and no clinical signs of heart disease may have minor abnormalities of left ventricular function as shown by echocardiography. Echocardiography is more sensitive than systolic time intervals in detecting these abnormalities; both systolic and diastolic function abnormalities, alone or together, can occur. There seems to be no relation between involvement of skeletal and cardiac muscle.

Myotonic muscular dystrophy is a diffuse systemic disorder, which is inherited as an autosomal dominant trait, with appearance in both sexes, generally late onset of symptoms, and slowly progressive evolution. The clinical picture may include involvement of skeletal and cardiac muscle, cataracts, premature frontal baldness, bone changes, testicular atrophy, other mild endocrine abnormalities, and mental deterioration.

Evidence of cardiac disease in patients with myotonic dystrophy is usually found in the electrocardiogram, the most common alterations being P and ST and T wave abnormalities, first degree atrioventricular block, left axis deviation, atrial flutter and fibrillation, bundle-branch block, and premature atrial and ventricular contractions (DeWind and Jones, 1950; Fisch, 1951; Cannon, 1962; Miller, 1962; Payne and Greenfield, 1963; Fearrington *et al.*, 1964; Church, 1967). There is still little information on the functional abnormality of cardiac muscle in these patients, because in the majority there is insufficient indication for invasive investigations such as cardiac catheterisation and angiocardiography. It has recently been suggested, however, that cardiac involvement in myotonic dystrophy is not merely common, but is an integral part of the condition, resulting from the complete expression of the gene towards striated muscle tissue, whether skeletal or myocardial (Schmitt and Schmidt, 1975).

We have, therefore, considered it of interest to study left ventricular function not only in patients with myotonic dystrophy in the early stages, but also in those relatives with no clinical signs of the disease, but who already had pathological changes in skeletal muscle. In order to avoid cardiac catheterisation, we have measured left ventricular dimension noninvasively by echocardiography (Chapelle and Mensch, 1969; Popp *et al.*, 1969); instantaneous left ventricular dimension was measured throughout the cardiac cycle along with its rate of change (Gibson and Brown, 1973).

Patients and methods

Seven patients (2 male and 5 female, age range 10 to 44 years) were studied. All had typical physical findings, and the diagnosis was substantiated by electromyography and positive skeletal muscle biopsies. In addition, the 3 children of one of them,

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Table *Skeletal muscle, echocardiograpic, and mechanocardiographic findings in 7 patients with myotonic dystrophy (cases 1 to 7) and in 3 children with family history of myotonic dystrophy (cases 8 to 10)*

Case No.	*Sex*	*Age (y)*	*Skeletal muscle involvement*	*Echocardiographic measurements*				*Systolic time intervals*			*RR interval*
				ESD *(cm)*	*EDD* *(cm)*	*Peak shortening rate** (s^{-1})	*Peak lengthening rate†* (s^{-1})	$Q\text{-}A_2$ *(ms)*	*LVET* *(ms)*	*PEP* *(ms)*	*(ms)*
1	F	12	Moderate	2·4	3·7	3·2	3·6	310	240	70	660
2	F	12	Mild	2·6	3·7	*1·9*‡	*1·8*	370	280	90	860
3	F	10	Mild	2·6	3·5	*1·9*	3·4	320	245	75	630
4	F	37	Moderate	2·8	4·0	*1·7*	2·5	390	290	100	780
5	F	44	Moderate	4·0	5·0	*1·4*	*0·8*	360	260	100	720
6	M	38	Moderate	3·0	4·1	2·8	2·4	340	250	90	630
7	M	12	Mild	2·5	3·6	2·6	5·0	360	270	90	700
8	F	8	Minimal	2·4	4·0	2·4	3·2	360	280	80	790
9	M	6	Minimal	2·2	3·6	3·4	4·1	310	240	70	600
10	M	11	Minimal	2·4	3·9	3·5	*2·0*	360	275	85	740

*Normal range: 2·0-3·6 s^{-1} in children, 1·8-3·2 s^{-1} in adults.
†Normal range: 2·2-5·5 s^{-1} in children, 2·0-5·5 s^{-1} in adults.
‡Abnormal values are in italics.

aged 6, 8, and 11 years, were also included in the study. Though these children had no clinical signs of myotonic dystrophy, muscle biopsies showed a selective hypotrophy and predominance of type I muscle fibres; ultrastructural studies showed dilatation of the sarcoplasmic reticulum and T tubules and sarcoplasmic masses without myofibrils within the muscular fibres. These findings were consistent with a very early stage of the disease (Scelsi *et al.*, 1977). The degree of skeletal muscle involvement was arbitrarily classified as *minimal* when only ultrastructural abnormalities were present, *mild* when muscular weakness and wasting only affected facial and proximal muscles, and *moderate* when muscular weakness and atrophy were generalised but interfered little with normal activity: there were no *severe* cases, in whom extreme difficulty in movement would have been present (Table).

Chest *x*-ray films and electrocardiograms were obtained in all the subjects, and systolic time intervals were also recorded as described by Weissler and associates (1968), immediately before the echocardiographic study. Total electromechanical systole (Q-A2), left ventricular ejection time (LVET), and pre-ejection period (PEP) were measured to the nearest 5 ms in at least 5 cardiac cycles and the means calculated.

Echocardiographic measurements were made with a Smith Kline Ekoline 20 ultrasonoscope, using a 2·25 MHz 1·25 cm transducer, and in all cases a simultaneous electrocardiogram was recorded. Clear continuous echoes of the endocardium were obtained on the left side of the septum and the posterior wall. The subjects were studied in the supine position or turned slightly to the left, with the transducer in the 3rd, 4th, or 5th interspace.

DIGITISATION

Echocardiograms were digitised as described by Gibson and Brown (1973), using a Summagraphics digitiser and a Prime 300 computer system at Brompton Hospital, London. Data points were generated for the endocardium of the septum and the posterior wall, together with calibration signals representing 0·5 s, 1 cm, and the RR interval of the beat to be studied. From the digitised data, using an incremental plotter, plots were made of left ventricular dimension (D), rate of change of dimension (dD/dt), and normalised rate of change of dimension $(1/D \times dD/dt) = Vcf$ in s^{-1} (Fig. 1). End-diastolic dimension was taken as that synchronous with the QRS complex of the electrocardiogram, and end-systolic dimension as the minimum of the left ventricular dimension curve. Peak systolic and diastolic rates of wall movement were estimated in normalised form. The echocardiographic and mechanocardiographic data are given in the Table.

CONTROL VALUES

Control values for the systolic time intervals were taken from a previous study of 260 normal subjects aged 11 to 54 years, in which the limits of variation were assessed by the tolerance ellipse method (Rampulla *et al.*, 1973).

The echocardiographic data were compared with those obtained in a normal population of 28 children, age range 6 to 12 years (T. F. Tse, unpublished observations), and in a normal population of 12 older subjects (Venco *et al.*, 1977). Normal ranges

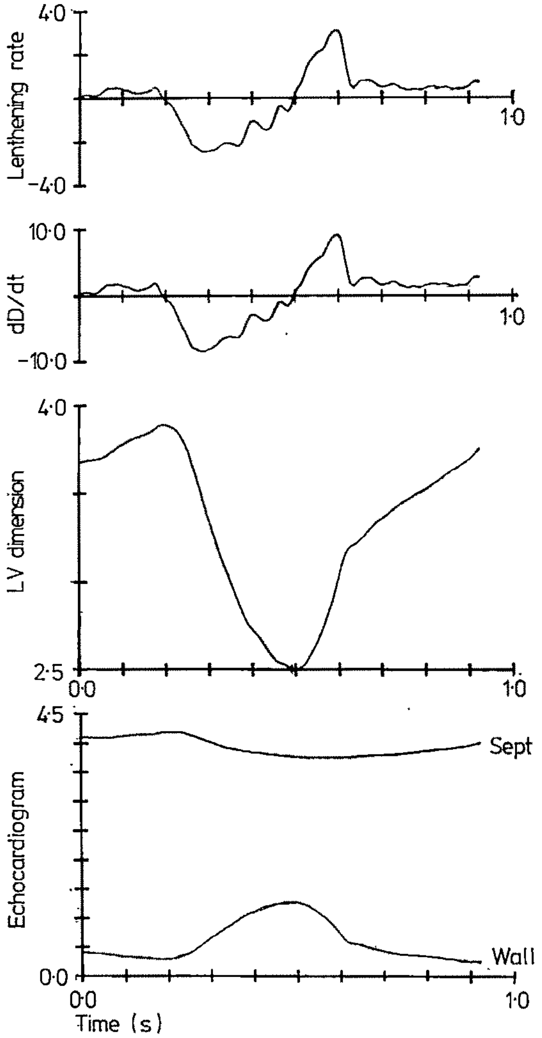

Fig. 1 *Computer output of digitised echocardiogram from case 8 showing (from below) the original data showing septum and posterior wall, left ventricular dimension, rate of change of dimension (dD/dt), and normalised rate of change of dimension. The cross on the dimension trace marks mitral valve opening.*

for peak shortening and lengthening rate of left ventricular internal dimension are given in the footnote to the Table.

Results

(1) CLINICAL

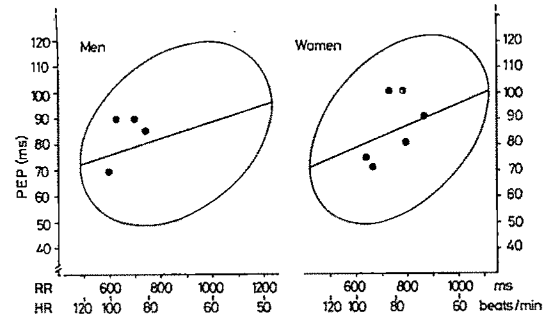

Fig. 2 *Tolerance ellipses and regression lines of pre-ejection period (PEP) relative to heart rate in 130 normal men and 130 normal females. The dots represent the values obtained in the subjects of the present study.*

Only one patient with myotonic dystrophy had clinical evidence of significant cardiac involvement, with dyspnoea on effort, an apical pansystolic murmur of grade 3/6, slight cardiomegaly on *x*-ray examination, and an electrocardiogram showing type B WPW pattern. All the remainder had normal chest *x*-ray films and electrocardiograms, though 2 had a soft systolic murmur.

(2) SYSTOLIC TIME INTERVALS

PEP and LVET were within normal limits in all 10 patients, as shown in Figs 2 and 3.

(3) ECHOCARDIOGRAPHY

Left ventricular dimensions at end-systole and end-diastole were normal in all subjects. Peak shortening rate, however, was reduced in 4 of the 7 patients with clinical disease, but not in the 3 children. In 2 of the patients and in 1 of the clinically unaffected children, peak diastolic lengthening rate was also reduced. These abnormalities were slight, except in case 5, in which there was clinical evidence of significant cardiac involvement. This patient also had type B WPW syndrome, but abnormalities of septal

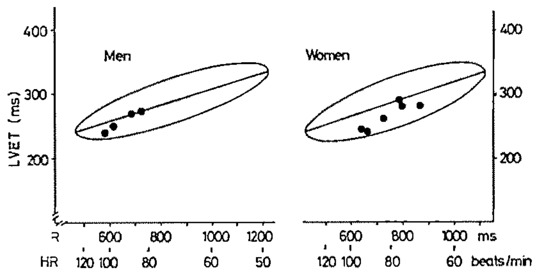

Fig. 3 *Tolerance ellipses and regression lines of left ventricular ejection time (LVET) relative to heart rate in 130 normal men and 130 normal women. The dots represent the values obtained in the subjects of the present study.*

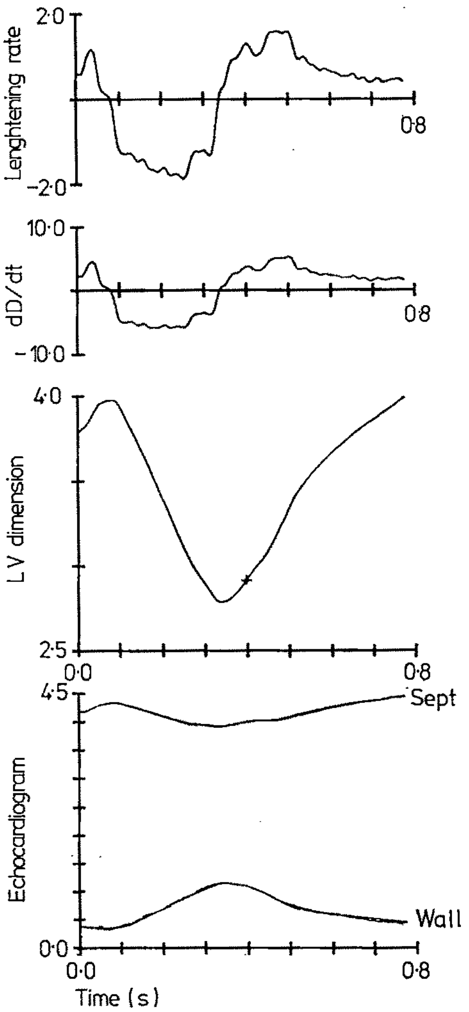

Fig. 4 *Computer output of digitised echocardiogram from case 2. The layout is similar to that of Fig. 1. There is a considerable reduction in peak shortening and lengthening rate of left ventricular dimension.*

movement (DeMaria *et al.*, 1976; Hishida *et al.*, 1976) were not present. Thus, 5 of the 10 subjects studied had some functional abnormality of left ventricular contraction or relaxation alone or together. Fig. 4 is from a patient (case 2) with impairment of both Vcf and lengthening rate.

Discussion

Cardiac involvement in myotonic muscular dystrophy was described by Griffith in 1911 and since then many other reports have appeared. Characteristically, cardiac abnormalities are recognised when the clinical manifestations of the disease are well advanced, but they are often the primary cause of death (Wolintz *et al.*, 1966). Necropsy studies have shown no characteristic histological pattern, but a varying amount of myocardial replacement with fat or fibrous tissue may occur (Fisch and Evans, 1954; Slatt, 1961; Cannon, 1962; Holt and Lambert, 1964). In addition, there is no apparent relation between the histological findings and the clinical severity of the heart disease (Holt and Lambert, 1964).

An abnormal electrocardiogram is usually considered the most important clue to the diagnosis of heart disease in such patients, but this was not the case in our series, where the electrocardiogram was abnormal in only one. This differs from previous experience, where electrocardiographic abnormalities have been commonly observed and may even precede changes in the skeletal muscle (Kuhn, 1960; Payne and Greenfield, 1963; Petkovich *et al.*, 1964; Wolintz *et al.*, 1966). The most likely explanation for this discrepancy lies in the very young age of almost all our subjects, 7 out of 10 being below 13 years of age.

A more specific and sensitive diagnostic tool seems necessary in the early stages of the disease. Fumagalli and Savoldi (1960) recorded systolic time intervals in 4 patients with myotonic dystrophy and found abnormal prolongation of isovolumic contraction time in all of them. However, systolic time intervals were normal in all our patients, including the one with clinical signs of heart disease (case 5), indicating the low sensitivity of this diagnostic procedure.

In the present study, therefore, we used echocardiography to assess left ventricular function. Left ventricular dimension at end-systole and end-diastole can be measured directly from the echocardiogram. These measurements were normal in all patients, including case 5 with clinical evidence of left ventricular disease. Further information can be obtained by digitisation of the original records, allowing peak rates of changes of dimension in systole and diastole to be calculated. Abnormalities of these were found in 4 patients with myotonic muscular dystrophy and in 1 child with a family history of the disease and an abnormal muscle biopsy, though there were no clinical signs of skeletal muscle involvement. Both contraction and relaxation of the left ventricle were involved, just as skeletal muscle shows the abnormalities of dystrophia and myotonia, affecting strength of contraction and velocity of relaxation, respectively. These findings, together with the normal internal dimensions of the ventricles, show that functional abnormalities of the heart appear well before anatomical abnormalities are clinically apparent.

Moreover, as was observed by Holt and Lambert (1964), no close relation seems to exist in our cases between involvement of skeletal and cardiac muscle; for example, case 1 was one of the most clinically affected patients, but no abnormalities of left ventricular function were apparent on echocardiography, and case 10, who had no clinical signs of myotonic dystrophy, had slight impairment of left ventricular relaxation.

In conclusion, echocardiography seems to be a useful method in the early diagnosis of cardiac involvement in patients with myotonic muscular dystrophy, when electrocardiograms and systolic time intervals are normal and even when no clinical abnormalities are present. Follow-up studies, which can easily be accomplished with this non-invasive technique, will probably cast some light on the natural history of cardiac involvement in myotonic muscular dystrophy.

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Muscle ridge between atrioventricular valves and malalignment of junction of these valves with ventricular septum

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SUMMARY A posteromedian muscle ridge is found in the left ventricle between the two atrioventricular valves in congenital malformations of the heart, where malalignment exists between the ventricular septum and the junction of both atrioventricular valve rings; this is seen in transposition with straddling tricuspid valve and double inlet ventricle with outflow chamber. In hearts with normal alignment of the atrioventricular valve and transposition of the great vessels, the same posteromedian muscle ridge was identified in all specimens with associated posterior ventricular septal defect without a muscular rim between the tricuspid valve and the edge of the ventricular septal defect. If this rim was present or if the ventricular septal defect was midseptal, only 50 per cent of the specimens studied showed a posteromedian muscle ridge. This muscle ridge was present in only 20 per cent of the hearts without a ventricular septal defect or with an anterior ventricular septal defect.

The posteromedian muscle ridge has a narrow cranial part (head) which is just apical from the junction of the atrioventricular valve rings or apical from the septum membranaceum or its remnants. The middle part (body) is wider and occasionally double, extending down the posteromedian side of the anterior leaflet of the mitral valve, on the dorsal free wall of the left ventricle, or in the angle between those two structures. It then branches out and joins the base of the posterior papillary muscle and an accessory papillary muscle, which holds the left ventricular part of the tricuspid valve.

The specimens studied showed a full range of malformations from uncomplicated transpositions, wherein the muscle ridge cannot or can scarcely be identified, to varying degrees of straddling tricuspid valve, wherein the valve moves further and further away from the septum, and finally to the double inlet ventricle of the left ventricular type, wherein the bulboventricular septum lies at the opposite side of the right atrioventricular valve.

In double inlet ventricle of the right ventricular type with left posterior pouch, both atrioventricular valves and the posteromedian muscle ridge crossed the septum and were found in the right ventricle.

In studying the left ventricle in transposition of the great arteries of the heart with straddling right atrioventricular valves and in double inlet ventricle, we noticed a large muscle ridge distal to the junction of the atrioventricular valve rings.

In published reports the attachments of the chordae tendineae of both atrioventricular valves have been described at length in cases of straddling tricuspid valve (Mehrizi *et al.*, 1966; De la Cruz and Miller, 1968; Rastelli *et al.*, 1968; Liberthson *et al.*, 1971; Tandon *et al.*, 1974). Little attention has been paid, however, to the relation of the valve annuli and the muscle ridge that separates them. Liberthson *et al.* (1971) described the condition thus: 'A median ridge either independent of or fused with the accessory posterior papillary muscle of the left ventricle often extended from the central fibrous body to the apex, on the posterior wall.' Recently Wenink *et al.* (1976) mentioned the presence of such a ridge in 35 per cent of transpositions without ventricular septal defect, in 80 per cent of transpositions with ventricular septal defect, and in 3·5 per cent of normal hearts.

The purposes of this study are (1) to describe in

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Table *Diagnosis of 137 specimens studied*

Diagnosis	*Specimens*	*Per cent with PMMR*
96 Transpositions	22 with intact ventricular septum	18
	16 with anterior ventricular septal defect	25
	58 with posterior or midseptal ventricular septal defect	
	36 with muscular rim between tricuspid valve and edges of ventricular septal defect	50
	22 without muscle rim	
	12 without straddling tricuspid valve	100
	10 with straddling tricuspid valve	100
13 Double inlet ventricle	10 with left ventricular morphology and anterior outflow chamber	
	7 with 2 atrioventricular valves	100
	3 with common atrioventricular valve	?
	3 with right ventricular morphology	100
	2 with left posterior pouch	
	1 without pouch	
28 Complete common atrioventricular canal		0

detail the posteromedian muscle ridge, (2) to define its presence and position in different types of transposition, in double inlet ventricle of the left and of the right morphological type, and in complete atrioventricular canal, and (3) to study the spectrum of straddling tricuspid valve.

Material and definitions

Ninety-six specimens of transposition of the great arteries, all from the Mayo Clinic, were studied (Table). In these specimens the ventricular septal defect was essentially a nonjunction between the infundibular septum and the ventricular septum (Goor and Edwards, 1973). The ventricular septal defect may extend posteriorly, anteriorly, or in both directions. When it extends posteriorly, the membranous septum is partly or completely missing and the muscular rim between the edge of the defect and the tricuspid valve is not always present. If this rim is absent, it is sometimes difficult to determine whether or not the tricuspid valve is straddling the septum.

In our study we grouped all defects extending posteriorly under the heading 'posterior ventricular septal defect.' In some cases the defect was situated in the middle of the muscular septum away from the valve annuli and was referred to as 'midseptal ventricular septal defect.' Infrequently the defect was exclusively anterior, sometimes extending into the infundibular septum. In such cases we used the term 'anterior ventricular septal defect'.

Thirteen specimens with double inlet ventricle (9 from the Mayo Clinic and 4 from Gent, Belgium) were also analysed. In 10 of them the ventricle had a left ventricular morphology and an anterior outlet chamber. Three double inlet ventricles showed right ventricular morphology and 2 of these had a small left posterior chamber with no inflow or outflow portion and a smooth septal surface. This pouch, however, did communicate with the large ventricle by way of a small septal defect (Table).

In addition a study was made of 28 hearts with a common atrioventricular canal (2 from the Mayo Clinic, 21 from Leiden, Holland, and 5 from Gent) (Table).

Results and description

In 4 of 10 specimens with posterior ventricular septal defect, with varying degrees of straddling of the tricuspid valve over the ventricular septum, the morphological right atrium was connected by a straddling tricuspid valve to a right-sided chamber with characteristics of the right ventricle, and a left atrium was connected by a mitral valve with a left-sided chamber with characteristics of the left ventricle (normally situated ventricles). All of these specimens had right-sided transposed aortas.

In the other 6 of these 10 specimens, the chamber with characteristics of the right ventricle was to the left of the chamber with left ventricular characteristics (ventricular inversion). In such hearts, the left atrioventricular valve straddles the septum, having characteristics of the tricuspid valve, and the transposed aorta is on the left side. The atrioventricular valve rings meet at the central fibrous body and are attached to it, the atrial septum being attached to the same structure. The ventricular septum does not join the central fibrous body in cases with straddling tricuspid valve but is more to the right in normally situated ventricles (Fig. 1) and to the left if the ventricles are inverted (Fig. 2 A). Just distal to the junction of both atrioventricular valve rings, a muscular structure protrudes into the left ventricular cavity (Fig. 1 and 2 A). This structure extends down the posterior wall of the left ventricle towards the apex and joins the posterior papillary

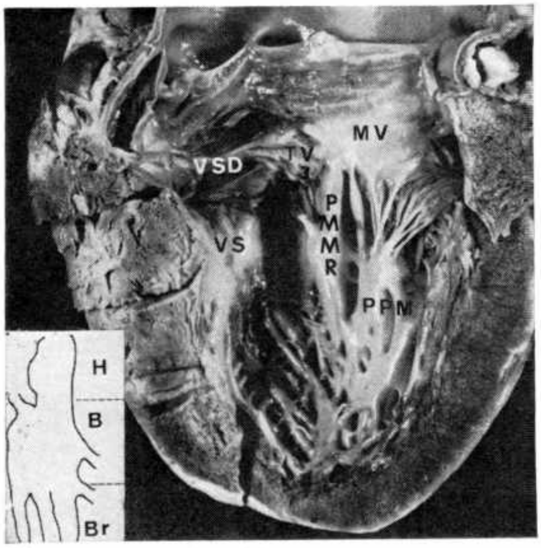
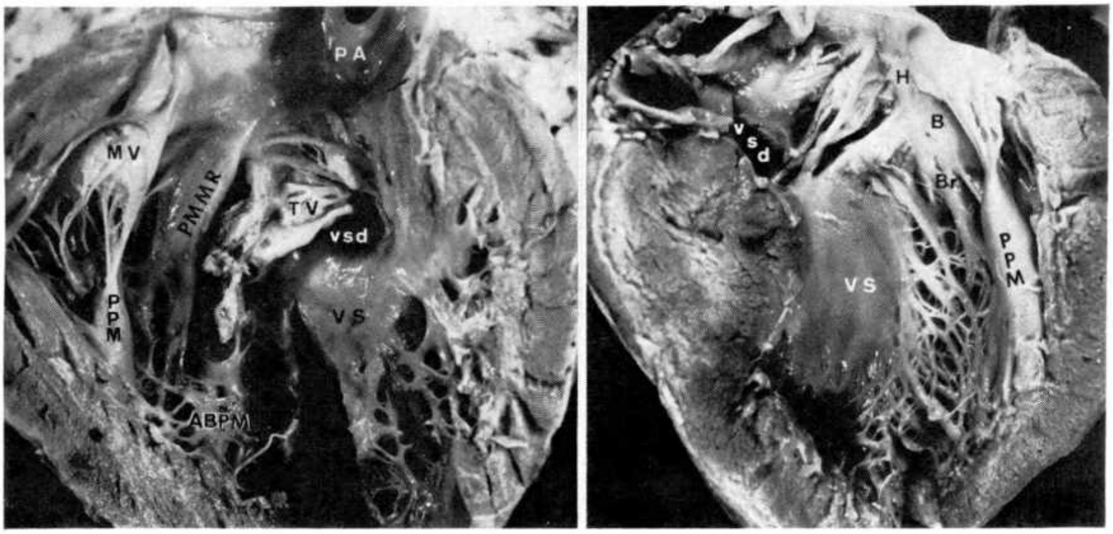


Fig. 1 *Transposition with aorta to right and anterior to pulmonary artery, posterior ventricular septal defect (VSD), and straddling tricuspid valve (TV): VSD to left; in middle, under junction of mitral valve (MV) and (TV), a posteromedian muscle ridge (PMMR), with narrow head (H), wider body (B), and branches (Br) (see inset) joining posterior papillary muscle (PPM) of ventricle.*

muscle of the left ventricle (Fig. 1). If an accessory or abnormal papillary muscle is present in the left ventricle to hold the chordae of the left ventricular part of the straddling tricuspid valve, the caudal end of the posteromedian muscle ridge extends between this accessory papillary muscle and the posterior papillary muscle and often has connections with both (Fig. 2 A).

Usually the posteromedian muscle ridge is narrow at its cranial end, known as 'the head' (Fig. 1), becomes wider and more protruding in its middle portion (the body), and then divides into several muscle bundles (branches), which become progressively smaller, finally appearing like small trabeculae at the site where they join the papillary muscles. Sometimes the accessory papillary muscle joins the median muscle already at its middle portion (Fig. 1). This middle portion is often double (Fig. 3 A).

When there is an extensive overriding of the tricuspid valve and the junction of both atrioventricular valve rings is displaced far away from the septum, this muscle is completely dissociated from the ventricular septum (Fig. 1). When the tricuspid valve is not straddling or is only slightly straddling, this muscle seems to glide off the septum



(*A*) Fig. 2 (*A*) *Transposition with aorta to left and anterior to pulmonary artery (PA) with inversion of ventricles and straddling tricuspid valve. In middle: junction of both AV valves (TV and MV) with large PMMR protruding underneath into left ventricular cavity and branching toward base of posterior papillary muscle (PPM) and to right toward base of an abnormal papillary muscle (ABPM) holding chordae of part of TV that lies in left ventricle.* (*B*) *Transposition with aorta to right and anterior to pulmonary artery and large posterior VSD: no muscular rim between tricuspid valve and edge of VSD. Head (H) of posteromedian muscle ridge (PMMR) between both atrioventricular valve (AVV) rings. Body (B) of this muscle extending from septum to posterior free wall of left ventricle and its branches (Br) joining base of PPM of left ventricle.* (*B*)

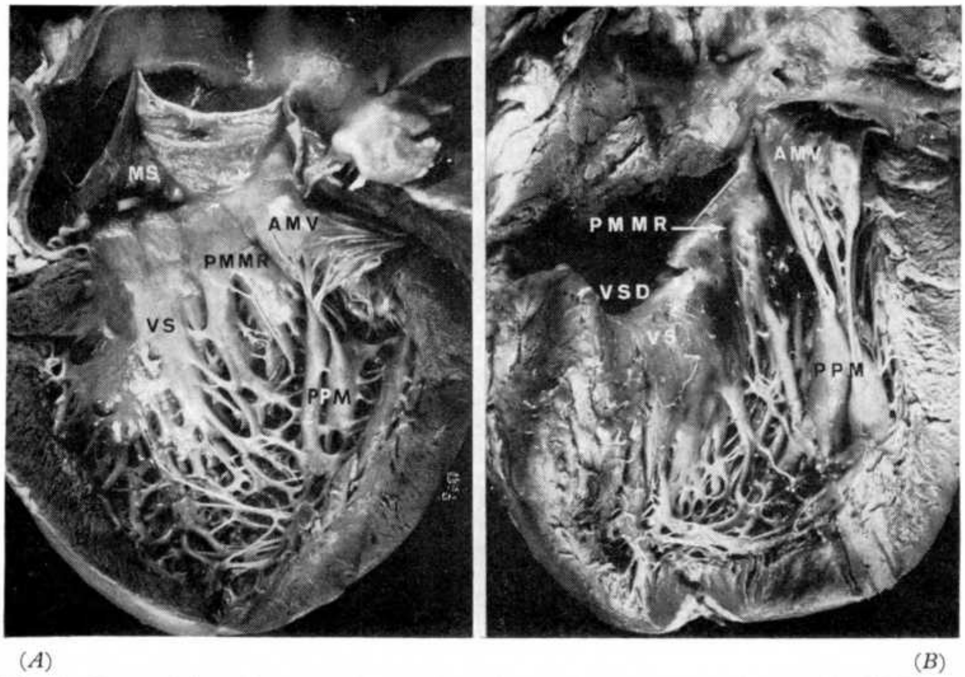


Fig. 3 *Transposition with aorta to right and anterior to pulmonary artery with posterior (VSD). (A) Under the membranous ventricular septum (MS) a posteromedian muscle ridge (PMMR) protrudes on the ventricular septum (VS), extending parallel to the anterior mitral valve leaflets (AMV) towards the base of the posterior papillary muscle (PPM) of the left ventricle. The body of the muscle splits up into two muscle bundles so that it looks like a double muscle body. (B) PMMR protrudes in an angle between VS and posterior left ventricular free wall. Head seems to be incorporated in posterior edge of VSD, while branches join base of PPM of left ventricle.*

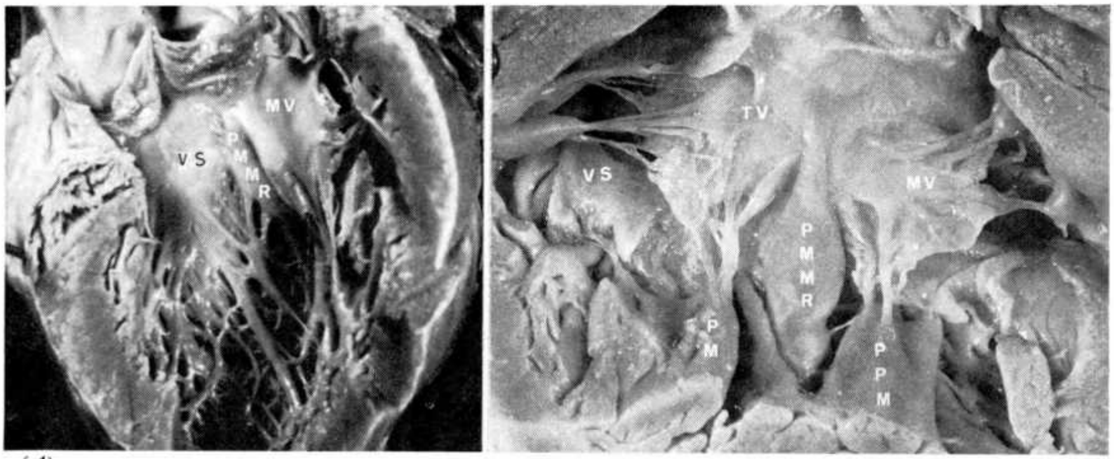
(Fig. 2 B). Its cranial insertion lies on the septum between the atrioventricular valves and its distal part goes toward the posterior wall of the left ventricle to reach the base of the papillary muscle.

The posteromedian muscle ridge could be identified in all cases with posterior ventricular septal defect and absence of a muscular rim between the tricuspid valve and the edges of the ventricular septal defect. In 14 of the 22 specimens the posteromedian muscle ridge was large. In some cases it was so large that it must have interfered, to some extent, with the flow of blood from the left ventricular body into the left ventricular outflow tract. The obstruction caused by such a ridge alone, however, may not be sufficient to produce a pressure gradient. It could add to the narrowing caused by other structures located more distally, such as the mitral valve apparatus and the anterolateral muscle described by Moulaert (1974).

In half of the specimens with a midseptal or a posterior ventricular septal defect with muscular rim between the tricuspid valve and the edge of the ventricular septal defect, a similar muscular structure was seen apically from the posterior margin of the membranous septum or its remnants (Fig. 3 A). The head of the muscle seemed to be incorporated in the septum, but the body extended either on the septum (Fig. 3 A) or into the angle made by the junction of the posterior wall and the ventricular septum (Fig. 3 B). The muscle continued parallel to and at the septal side of the anterior leaflet of the mitral valve (Fig. 3 A). The branches also pointed to the posterior papillary muscle and sometimes joined it.

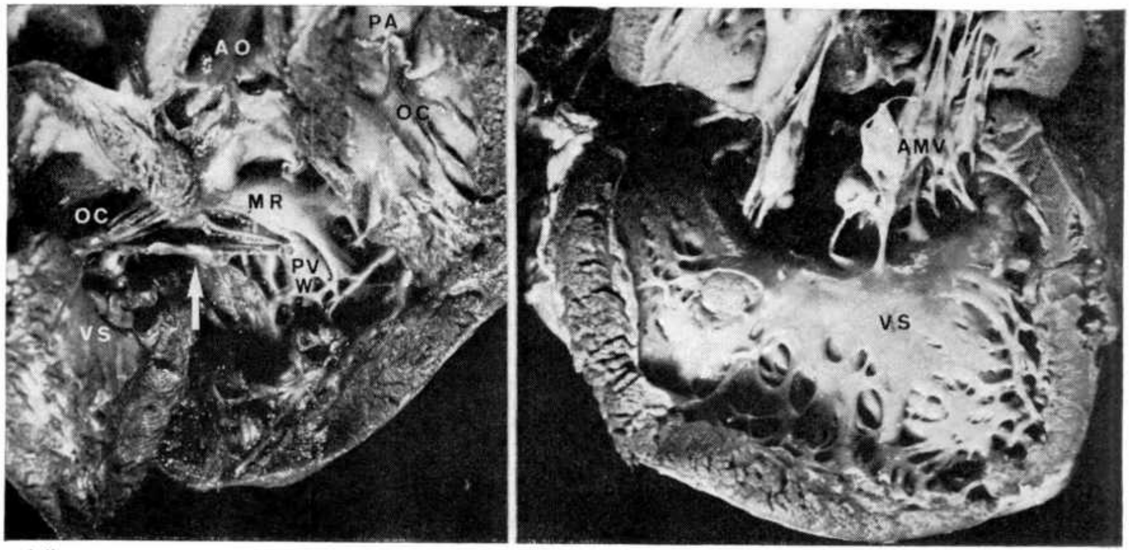
When the ventricular septal defect is purely anterior or when the ventricular septum is intact, this median muscle ridge is not prominent (Fig. 4 A); it could be identified, however, in 21 per cent of our specimens.

In double inlet ventricle with left ventricular morphology and outlet chamber the posteromedian muscle ridge is also present and seems to anchor the atrioventricular valves to the posterior wall far away from the septum (Fig. 4 B). In a single case with common atrioventricular valve, a muscle similar to a posteromedian muscle ridge was found. It was



(*A*) (*B*)

Fig. 4 (*A*) *Transposition with aorta to right and anterior to pulmonary artery and without ventricular septal defect (VSD). View of left VS, anterior mitral leaflet, and opened pulmonary artery. A small posteromedian muscle ridge (PMMR) dissociates itself from the ventricular septum (VS) and continues down along the mitral valve (MV) in an angle between VS and posterior free wall toward base of posterior papillary muscle (PPM) of left ventricle.* (*B*) *Double inlet ventricle with aorta originating from outlet chamber right anterior of pulmonary artery. On the posterior ventricular free wall a PMMR extends from the junction of both AV valves (TV and MV) to the base of the papillary muscle (PM), far away from the ventricular septum (VS).*



(*A*) (*B*)

Fig. 5 (*A*) *Double inlet ventricle with common atrioventricular valve (AVV) and left anterior outlet chamber (OC). Left, anterior part of ventricle, VS, and OC. Right, posterior part of ventricle and OC with pulmonary artery (PA). In middle, common AV valve is stretched out (white arrow); cranially and in the centre of this valve a muscle ridge (MR) is attached to it; from there the muscle ridge extends down the posterior free wall of the ventricle (PVW) to the base of the posterior papillary muscles.* (*B*) *Common atrioventricular canal. View of left side of ventricular septum (VS) and deformed anterior mitral valve (AMV). No median muscle ridge.*

related to the posterior cusp of the valve, anchoring it to the posterior wall of the left ventricle where the atrial septum emerged on the atrial side (Fig. 5 A). From there it extended down toward the posterior papillary muscle. The anatomy in this case, however, was so bizarre that it was not possible to identify the muscle as the posteromedian muscle ridge.

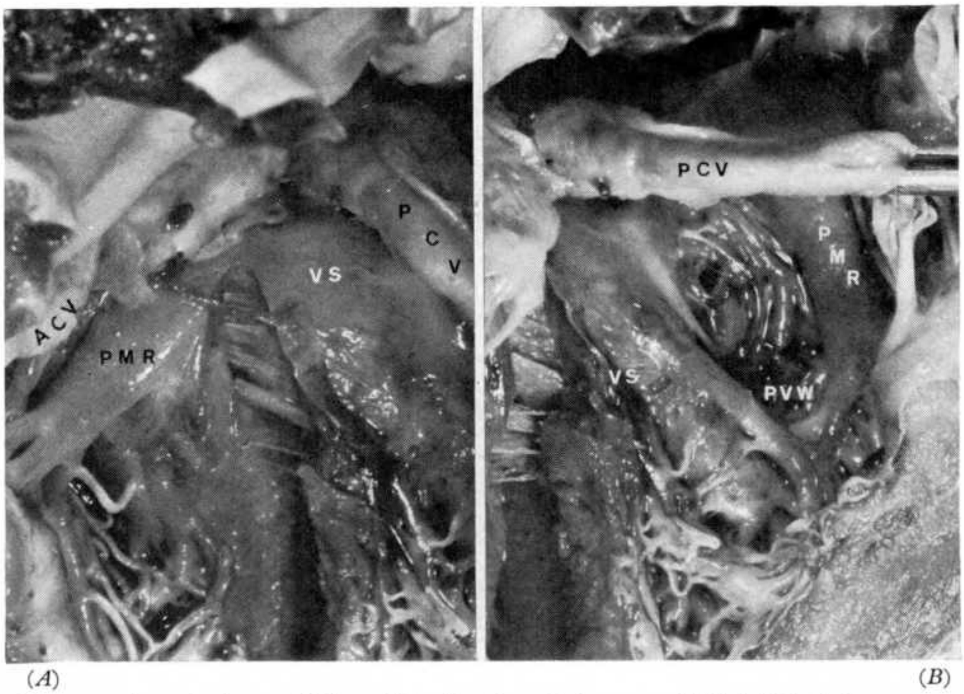
In the 3 cases of double inlet ventricle with right ventricular morphology a small but distinct posteromedian muscle ridge was found distal to the junction of the two atrioventricular valve rings. It had a distorted aspect in the sense that head, body, and branches did not lie in a straight line but in a curved line that had its convexity toward the right. The branches did join the posterior papillary muscles of both atrioventricular valves. The head and part of the body of the posteromedian muscle ridge formed the right posteroinferior edge of the communication of the large ventricle with the diminutive chamber. The posteromedian muscle ridge seemed to be a good landmark for location of the entrance to this pouch.

Twenty-eight specimens of complete common atrioventricular canal were studied to ascertain the presence or absence of the muscle ridge when fusion of the atrioventricular cushions was lacking. It was not possible to identify any structure resembling the posteromedian muscle ridge in two-thirds of the hearts with complete common atrioventricular canal (Fig. 5 B).

On lifting up the posterior part of the anterior common leaflet in a third of the specimens, however, a small muscle ridge was identified extending from the atrioventricular valve ridge ring down the free wall of the left ventricle. This muscle had no distinct head, but its branches joined the posterior papillary muscle of the left ventricle (Fig. 6 B). In 2 cases a similar decapitated muscle ridge was present beneath the anterior part of the split anterior common leaflet as well (Fig. 6 A). In none of our 28 cases was the so-called head of the posteromedian muscle ridge present.

Discussion

The fact that a posteromedian muscle ridge is not prominent in hearts without a ventricular septal defect or pure anterior ventricular septal defect, but is well developed in hearts in which it is sited away



(*A*) (*B*)

Fig. 6 *Common atrioventricular canal. View of left side of ventricular septum (VS). (A) On lifting up anterior leaflet of common atrioventricular valve (ACV) a muscle ridge (PMR) is detected continuing down the anterior part of VS to the base of the anterior papillary muscle of left ventricle. (B) Under posterior leaflet of common atrioventricular valve (PCV) another muscle ridge (PMR) extends down the posterior free wall (PVW) of the left ventricle joining the base of the posterior papillary muscle of the left ventricle.*

from the septum suggests that the flow, entering the left ventricle on both sides of the posteromedian muscle ridge, creates a favourable situation for the muscle body to develop by a process of diverticulation and undermining in the same way as suggested for the development of papillary muscles (Netter, 1969).

The head of the posteromedian muscle ridge maintains a constant relation with the junction of the two atrioventricular valve rings even if this junction is sited away from the ventricular septum on the posterior left ventricular wall or in the right ventricle. If the septum separates the valves, the head seems to be part of the septum located just apical and posterior from the septum membranaceum (Fig. 3 A). The cranial insertion of the posteromedian muscle ridge is always situated where the atrial septum joins the central fibrous body.

On comparing specimens of transposition without ventricular septal defect (Fig. 4 A) or with anterior ventricular septal defect (Fig. 3 A) and those with posterior ventricular septal defect (Fig. 2 B), it is noted that the posteromedian muscle ridge detaches itself from the septum and becomes more and more prominent as the defect becomes more posterior. In specimens with posterior ventricular septal defect in which the muscular rim between the edge of the ventricular septal defect and the tricuspid valve is missing, it is difficult to determine whether or not the tricuspid valve is straddling the septum (Fig. 2 B). In these instances the posteromedian muscle ridge glides off the septum into the left ventricle, taking the tricuspid valve with it. The straddling of this valve becomes more and more obvious (Fig. 2 A). Finally, there is only a small part of the right atrioventricular valve left in the remaining part which we can no longer term a 'right ventricle' because it has practically no inlet (Fig. 7). This is the last step toward the formation of the anomaly of double inlet ventricle of the left ventricular type with outlet chamber (Fig. 4 B).

One can speculate that normal migration of the bulboventricular septum toward the atrioventricular canal during normal development follows the opposite direction, as we have described. Then the separation of the posteromedian muscle ridge from the ventricular septum means a splitting up of the ventricular septum into the derivatives of bulboventricular septum and the derivatives of atrioventricular canal septation. This hypothesis is reinforced by the fact that in the complete atrioventricular canal where such septation did not occur, the head of the muscle was not found in any of the 28 specimens.

The cases of double inlet ventricle of the right ventricular type could be the end point of another spectrum, that of the straddling of the mitral valve over the ventricular septum. Here the derivates of atrioventricular canal septation and ventricular septum do meet and even pass each other so that both atrioventricular valve rings and the posteromedian muscle ridge are in the right ventricle.

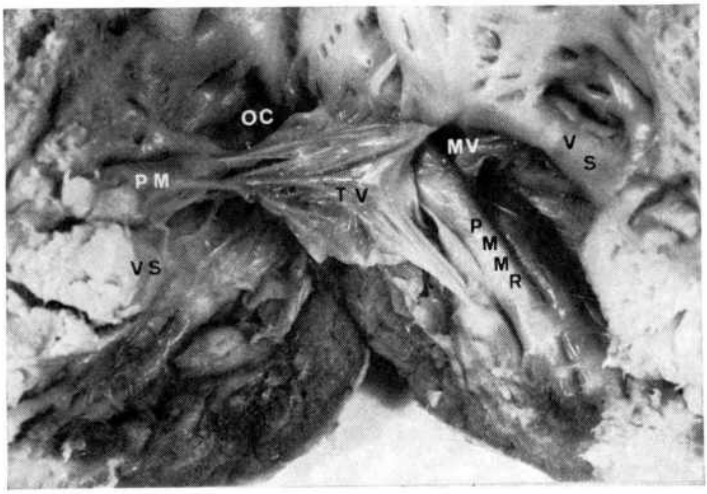


Fig. 7 *Double inlet ventricle with hypoplastic mitral valve (MV), left anterior outlet chamber, and pulmonary valve atresia. Left, anterior part of ventricle, ventricular septum (VS), and outlet chamber (OC). Right, posterior part of ventricle, VS, and OC; hypoplastic MV and PMMR between TV and MV. Centre, large tricuspid valve with papillary muscle joining PMMR; another papillary muscle (PM) crosses VS and is attached to the free wall of OC.*

In double inlet ventricle with outflow chamber, the muscle ridge between the two atrioventricular valves demarcates the two inflow tracts and is an ideal ridge on which to suture the septating patch. It has recently been shown that this ridge does not carry the conduction tissue in double inlet ventricle with an outflow chamber (Anderson *et al.*, 1974; Maloney *et al.*, 1975); suturing in this region, therefore, is a safe procedure.

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Ebstein's anomaly in persistent common atrioventricular canal

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SUMMARY This report documents 2 patients who presented with cyanosis early in life. In both instances the necropsy showed the simultaneous occurrence of an incomplete type of persistent atrioventricular canal and an Ebstein's malformation of the 'tricuspid' valve component. In the first patient no clinical investigations were done. In the second patient the electrocardiogram was consistent with persistent atrioventricular canal and the angiocardiogram showed the characteristic goose-neck deformity. Moreover, an abnormality of the right cardiac contour was seen, which in retrospect was correlated with the right-sided Ebstein's malformation. Ebstein's anomaly may significantly alter the clinical and haemodynamic profile of atrioventricular canal and should be considered in atypical cases. The presence of Ebstein's anomaly will complicate surgical repair of the atrioventricular canal.

Persistent common atrioventricular canal may occur in association with a wide variety of additional congenital heart malformations. However, the simultaneous occurrence of persistent common atrioventricular canal with Ebstein's anomaly of the tricuspid part of the valve is extremely rare. As far as we are aware only 2 cases have been described to date (Kilby *et al.*, 1956; Lev *et al.*, 1961). In both instances an incomplete form of atrioventricular canal was present and the Ebstein's anomaly was recognised during operation and at necropsy, respectively.

It is our purpose to document 2 cases of incomplete atrioventricular canal associated with Ebstein's anomaly of the tricuspid component. In one of these cases an angiographic-pathological correlation was made, a documentation which has not been published to date.

Report of patients

CASE 1

This male patient was born after an uneventful pregnancy and delivery; shortly after birth he developed respiratory distress accompanied by episodes of cyanosis. A heart murmur was noted. On admission he showed signs of severe heart failure. No further investigations could be performed and the child died at 5 days of age.

Necropsy showed major abnormalities confined to the heart and lungs. The heart was normally positioned in the thorax and had a normal arrangement with respect to segmental connections. Both atria were enlarged. There was an incomplete type of common atrioventricular canal, with a large defect of the primum type (Fig. 1). On the left side the septal leaflet showed a cleft separating an anterior from a posterior component. Both components originated directly from the crest of the septum, not permitting an interventricular communication (Fig. 1B). The valve was otherwise normally inserted into the left-sided annulus fibrosus. The right-sided valve leaflets, on the other hand, showed an additional abnormality consistent with that described in Ebstein's anomaly of the tricuspid valve. The septal leaflet of the right-sided component showed distinct downward displacement, starting at the site where the left-sided cleft reached the ventricular septum. The line of 'origin' of the displaced valve leaflet took a course posteriorly and apically, close to the trabecula septomarginalis, extending on to the inferior wall of the right ventricle, where it gradually veered back towards the atrioventricular annulus reaching it at the site of the margo acutus (Fig. 1A). A large atrialised part of the right ventricle was thus created (Fig. 1A). Moreover, part of the dis-

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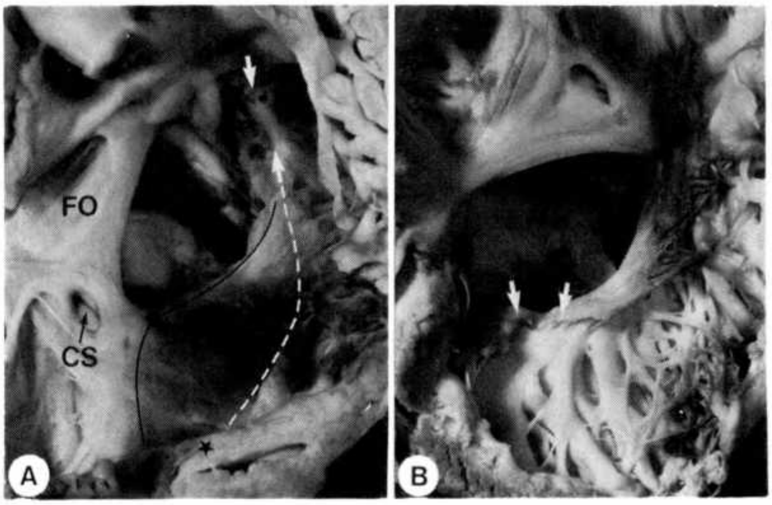

Fig. 1 *Case 1. (A) Opened right side of the heart. There is obvious distal displacement of the septal and inferior attachments of the tricuspid valve component (dotted line); compare with site of annulus fibrosus (solid line). A large atrialised part of the right ventricle is formed (between dotted and solid lines). A bare area (between arrows) is present between the displaced septal leaflet and the anterior 'tricuspid' component. Note that part of the inferior leaflet is muscularised (asterisk). A large primum type atrial septal defect is present, through which left heart structures are visible. CS, ostium of coronary sinus; FO, fossa ovalis. (B) Opened left side of the heart. The mitral valve component reveals a deep cleft (arrows), reaching to the crest of the ventricular septum and dividing this valve component into an anterior and a posterior part.*

placed valve leaflet was muscularised. A 'bare area' was present between the displaced septal leaflet and the anterior 'tricuspid' component. The latter took its 'origin' in a normal fashion from the annulus fibrosus, but the valve leaflet itself was curtain-like with direct insertions into right ventricular muscular trabeculae. The right ventricular infundibulum was normal, whereas the left-sided outflow tract was much narrowed because of the deficient ventricular septum and the firmly attached anterior leaflet. The great arteries showed no abnormalities; the ductus arteriosus was probe patent.

The lungs were congested and microscopical examination showed distension of pulmonary veins with a suggestion of 'arterialisation'.

CASE 2

Since birth this girl had had feeding difficulties caused by cheilognathopalatoschisis. The child was admitted to hospital at the age of 2 months because of progressive dyspnoea and cyanosis. Physical examination showed slight cyanosis at rest, but no signs of heart failure. Auscultation disclosed normal first and second heart sounds; there was no splitting of the second sound. A high frequency holosystolic murmur, grade 2/6, was noted. Both femoral arteries pulsated well. The plain chest film showed an egg-shaped, slightly enlarged heart with a left-sided aortic arch, a normal pulmonary segment and normal pulmonary vascular markings with no pulmonary venous congestion. The electrocardiogram showed a sinus tachycardia of 150 beats/min and signs of left ventricular hypertrophy. The electrical axis in the frontal plane was directed to the left. At cardiac catheterisation the right ventricle and pulmonary artery were not reached; there was a right-to-left shunt at atrial level with an arterial saturation of 73 per cent. Angiography showed a goose-neck deformity of the left ventricular outflow tract (Fig. 2A) and a small left-to-right shunt at ventricular level (Fig. 2B). Contrast injection into the right atrium showed an enlarged right ventricle, while the lateral projection of this injection revealed an indentation in the inferior border of the right ventricular cavity, dividing it into a smoothly outlined basal part and a trabeculated apical part (Fig. 3A). A normally positioned pulmonary trunk was visualised. At that time the malformation was not considered operable and the child was treated

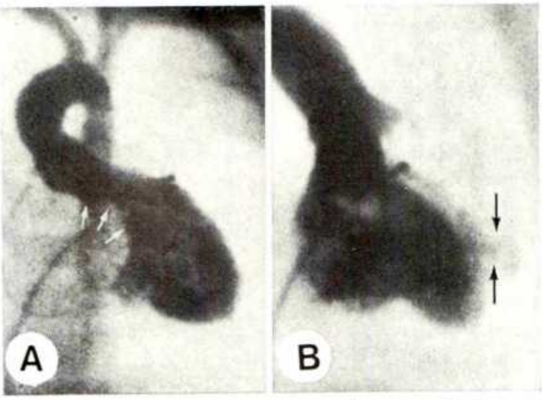

Fig. 2 *Case 2. Left ventricular angiogram. (A) Anteroposterior view revealing the goose-neck deformity (arrows) of the LV outflow tract. (B) In the lateral view a small left-to-right shunt (between arrows) is visible.*

medically. However, she gradually developed progressive heart failure and died at the age of 2 years.

Necropsy showed that the major abnormalities were confined to the heart and lungs. There was an incomplete form of persistent atrioventricular canal, with enlargement of both atria. The atrial septum showed a huge defect of the primum type, in addition to a fenestrated fossa ovalis (Fig. 4A and B). The left-sided atrioventricular valve showed an incomplete cleft in the septal leaflet (Fig. 4B). The outflow tract of the left ventricle was narrowed with a high insertion of the anterior part of the septal mitral valve component, in accordance with the clinical observation of a goose-neck deformity (Fig. 2A and 4C). The right-sided atrioventricular valve showed distinct downward displacement which was present over the septum and extended on to the inferior wall (Fig. 4A). The valve 'origin' came back to the annulus fibrosus at the level of the margo acutus. The anterior leaflet was normally inserted but curtain-like with localised muscularisation. A bridge of valve tissue was present between the displaced septal part, where it attached to the crest of the ventricular septum, and the anterior leaflet, thus creating a superior small 'extra' ostium with a diameter of 10 × 5 mm. Because of the abnormal 'origin' of the septal and inferior parts of the 'tricuspid valve' a large atrialised part of the right ventricle was formed. In retrospect it is clear that the atrialised part of the right ventricle corresponds with the smooth walled segment of the right ventricle seen on the angiogram (Fig. 3). A small muscular ventricular septal defect was present through which the left ventricle was connected to the inflow part of the right ventricle, immediately apical to the displaced septal leaflet (Fig. 2B and 4C). Both right and left coronary arteries had their ostia positioned above the right anterior aortic cusp. The left coronary artery took its origin from the posterior ostium and coursed posteriorly to the aorta after which a normal distribution pattern occurred.

The lungs were congested. Microscopical examination showed that the pulmonary veins had a very

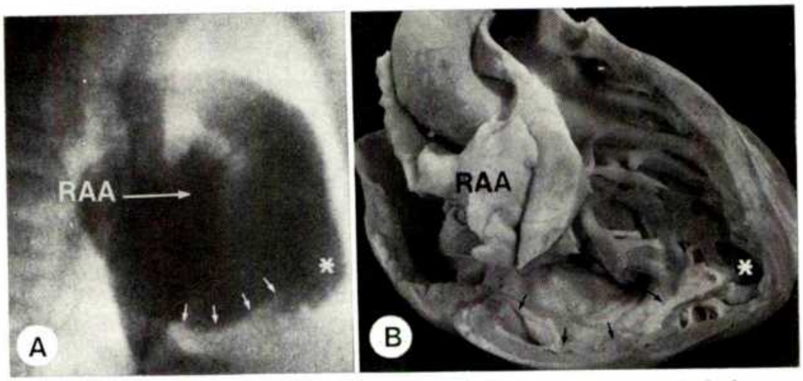

Fig. 3 *Case 2. Correlation between right heart angiogram and pathological anatomy. (A) Lateral view of the right-sided angiogram. The inflow part of the right ventricle shows a smooth inferior border (arrows) separated by an indentation from a trabeculated apex (asterisk). (B) The opened right side of the heart of this patient, viewed in similar direction. The smooth inferior border of the inflow part of the right ventricle (arrows) is caused by atrialised right ventricle, from Ebstein's anomaly of the tricuspid valve component. RAA, right atrial appendage.*

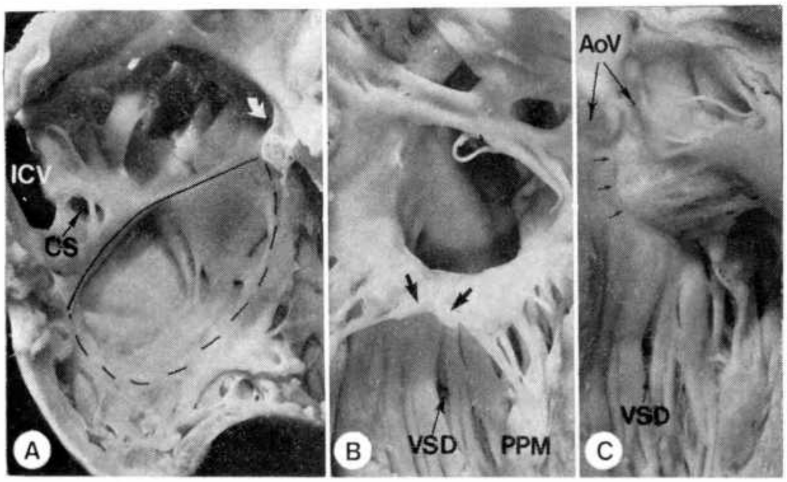

Fig. 4 *Case 2. (A) Opened right heart showing a large atrialised part of the right ventricle caused by distal displacement of the septal and inferior attachments of the tricuspid valve component (dotted line); compare with site of annulus fibrosus (solid line). A superior 'extra' ostium, barely visible (arrow), is created because of a bridge of valve tissue between the septal and anterior 'tricuspid' valve components. There is a large primum type atrial septal defect through which left heart structures are visible. The fossa ovalis is fenestrated. CS, ostium of coronary sinus; ICV, ostium of inferior caval vein. (B) The left side of the heart reveals a shallow cleft (arrows) in the 'mitral valve', a large primum type atrial septal defect and a fenestrated fossa ovalis. A muscular ventricular septal defect is present (VSD; compare with Fig. 2B). PPM, posterior papillary muscle. (C) Outflow segment of the left ventricle with high insertion of the anterior part of the septal mitral valve component (arrows), contributing to a narrowed outflow tract (compare with Fig. 2A). VSD, ventricular septal defect; AoV, aortic valve.*

hypertrophic media with 'arterialisation' of the wall. The pulmonary arterioles were slightly thin walled. Fibrosis was present in septa and subpleurally.

Discussion

The combination of Ebstein's anomaly of the 'tricuspid' valve with persistent common atrioventricular canal is rare. To the best of our knowledge this condition has been reported only twice previously. Kilby and associates (1956), in a clinical study on Ebstein's malformation, reported a 13-year-old girl (their case 9) with this combined malformation. Catheterisation had shown a large atrial septal defect with a predominant left-to-right shunt, while the course of the catheter suggested a low lying defect. Surgical exploration disclosed an incomplete form of persistent atrioventricular canal, in addition to Ebstein's anomaly of the septal 'tricuspid' valve component. The surgeon palpated a narrowed mitral valve, which might have contributed to the presence of a large left-to-right shunt. The child died, but necropsy was not permitted.

The second published report is that by Lev and associates (1961). They described the association of a 'Fallot-type' ventriculoarterial relation with persistent common atrioventricular canal. In one of their patients, a 1-month-old male infant (case 1), an Ebstein-like malformation of the right-sided valve component was found at necropsy. The valve showed displacement of the septal and inferior parts and dysplasia of the anterior leaflet. Again, an incomplete form of persistent atrioventricular canal was present. The child had been admitted to hospital because of dyspnoea and cyanosis since birth.

CLINICAL IMPLICATIONS

The combination of Ebstein's anomaly of the 'tricuspid' valve with persistent common atrioventricular canal is of practical significance. Of the two conditions it is most likely that the persistent atrioventricular canal will be diagnosed first. However, patients with persistent atrioventricular canal nearly always present with signs of a left-to-right shunt; cyanosis as an early symptom is rare (Ongley *et al.*, 1976) and may indicate an additional right heart problem. The patients described by Lev and associates (1961), presenting with a 'Fallot-type' morphology, are perfect examples in this respect and we suggest that Ebstein's anomaly of the tricuspid valve component should also be included among the possible diagnoses. In atrioventricular canal defects severe symptoms in infancy are always associated with one or more of the following factors: a large left-to-right shunt, severe mitral regurgitation, and significant associated cardiac malformations (Ongley *et al.*, 1976). Therefore, if an infant with an atrioventricular canal defect has severe and progressive symptoms, in the absence of a large left-to-right shunt or severe mitral regurgitation as in our second patient, complicating malformations should be suspected and looked for.

Recognition of these features is of particular significance since when 'persistent common atrioventricular canal' is diagnosed the main interest is focused on the left side of the heart. For diagnostic purposes left ventricular angiograms are mandatory while for surgical correction left ventricular dimensions and detailed visualisation of the 'mitral' valve component are vital. A complete and detailed study of the right side of the heart is considered unnecessary for either purpose. Even with reflux into the right atrium further study of the right-sided valve components is unnecessary, since it has been shown that in the majority of cases the regurgitation is caused by leakage of the left-sided atrioventricular valve.

Our present observations re-emphasise the fact that Ebstein's anomaly of the right-sided valve may coexist with the incomplete form of persistent atrioventricular canal and that this abnormality may play an important role in altering the haemodynamics and symptoms. As an example both infants were cyanotic early in life, a very uncommon finding with incomplete atrioventricular canal. It is obvious, moreoever, that the presence of Ebstein's anomaly will complicate surgical repair of atrioventricular canal.

We are indebted to Dr Niehuisen, Stichting St Elisabeth Ziekenhuis, Sluiskil, for the clinical data on case 1.

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Surgical treatment of persistent truncus arteriosus in the first year of life[1, 2]

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SUMMARY Between October 1974 and December 1977, 17 infants with persistent truncus arteriosus were admitted to this unit. Four had gross heart failure and severe metabolic acidosis. Two of these also had an interrupted aortic arch. All 4 died without operation. An urgent or semi-urgent correction was performed in 12 infants. Operations were done on cardiopulmonary bypass with deep hypothermia and circulatory arrest or periods of reduced flow. Continuity between the right ventricle and the pulmonary artery was established with a valved conduit (either fresh aortic homograft or porcine xenograft). Seven infants (aged 28 days to 8 months, weight 2·4 to 5·7 kg) survived the operation and are progressing satisfactorily. The causes of death in 5 infants are analysed. In addition, an 11-month-old infant with raised pulmonary arteriolar resistance died after operation. The lung histology showed grade III pulmonary vascular obstructive disease. The policies of medical treatment alone, palliation followed by correction, and early primary repair, are analysed on the basis of published data and our own results. It is concluded that the chances of a child surviving with a normal or near normal pressure in the pulmonary artery are best when the policy of early primary repair is followed.

Persistent truncus arteriosus is a rare congenital anomaly (Keith *et al.*, 1967): Collett and Edwards (1949) and Van Praagh and Van Praagh (1965) published detailed analyses and classifications of patients. Surgical correction of this condition was introduced in 1967 by McGoon and colleagues (1968). Provided pulmonary vascular disease is not severe, the results of correction in older children are excellent (Marcelletti *et al.*, 1977). However, most patients with persistent truncus arteriosus present in severe heart failure in the first days or weeks of life (Singh *et al.*, 1976). Many die despite intensive medical treatment. The median age at death was only 5 weeks in a series of 100 patients studied at necropsy by Calder and colleagues in 1976.

The published results of palliative surgery are also discouraging. A review by Poirier and colleagues (1975) showed that 43 out of 76 patients with persistent truncus died after pulmonary artery banding (56%). The mortality rate may be even higher as single unsuccessful operations are not usually reported.

For these reasons, we decided in October 1974 to offer 'corrective' operations to all infants with heart failure unresponsive to medical treatment, irrespective of age and weight (Singh *et al.*, 1975). The results in the first 4 infants have already been reported (Singh *et al.*, 1976). The purpose of this paper is to review our overall experience during a 3-year period and to discuss some of the problems of treatment of persistent truncus arteriosus in the first year of life.

Subjects and results

Persistent truncus arteriosus is defined here as that condition in which a single arterial trunk leaves the heart via a single semilunar valve and which gives rise directly to the coronary, systemic, and one or both pulmonary arteries (Crupi *et al.*, 1977). Between October 1974 and December 1977, we have seen 17 infants with persistent truncus. These have been divided into three groups.

GROUP 1: DIED BEFORE REPAIR (TABLE 1)

Four patients were admitted in gross heart failure and with severe metabolic acidosis. Two

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Table 1 *Truncus arteriosus in infancy — group 1*

Age	*Origin of pulmonary arteries*	*Additional cardiac anomalies*	*Comment*
2 d	Pulmonary trunk	VSD + TVR + interrupted aortic arch + 'criss-cross heart'	Death at 6 days: low cardiac output
4 d	Widely separate origin from truncus at different levels	PDA + interrupted aortic arch	Death on operating table: banded PA, PDA infiltration with formaldehyde; subarachnoid haemorrhage
8 d	Pulmonary trunk	VSD + PFO	Death at cardiac catheterisation: subarachnoid haemorrhage, infarcted kidney and bowel
8 d	Pulmonary trunk	VSD + PFO	Death at cardiac catheterisation: severe acidosis

VSD, ventricular septal defect; PFO, patent foramen ovale; PA, pulmonary artery; TVR, truncal valve regurgitation; PDA, persistent ductus arteriosus.

arrested and died during cardiac catheterisation. A third patient was admitted at the age of 2 days and was found to have severe truncal valve regurgitation, with type I truncus arteriosus; in addition there was interruption of the aortic arch and 'criss-cross heart' (Anderson *et al.*, 1974). The infant was in a low output state, which probably contributed to the severe burns suffered during attempts to rewarm after cardiac catheterisation. The fourth patient had persistent truncus arteriosus with widely separated pulmonary arteries, a persistent ductus arteriosus, and interrupted aortic arch.

GROUP 2: CORRECTION FOR INTRACTABLE HEART FAILURE (TABLE 2)

An urgent or semi-urgent operation was performed in 12 infants in intractable heart failure. Seven survived the operation and are progressing satisfactorily.

A 5-day-old infant was admitted moribund in severe heart failure with gross metabolic acidosis. The arterial pH remained below 7·0 despite massive doses of sodium bicarbonate and trometamol. Intensive treatment with catecholamines, diuretics, and assisted ventilation did not improve the child's condition. She started to convulse and became anuric. An urgent operation was uneventful despite the presence of left superior vena cava and some truncal valve regurgitation. Peritoneal dialysis was instituted immediately after operation, but despite this intensive treatment the infant deteriorated. Acidosis persisted, she developed disseminated intravascular coagulation, and died 12 hours after operation.

An 8-day-old infant had a massive intramyocardial injection during angiocardiography. Tamponade was relieved by an emergency operation, but at the completion of the repair the left ventricle did not contract and the infant died on the operating table. It was presumed that the damage to the left ventricular myocardium was responsible for this unfortunate outcome.

A 17-day-old infant died one day after operation. Excessive bleeding and partial compression of the conduit were probably major factors.

Another death occurred in a 5-month-old child with a very unusual anatomy. The right pulmonary artery, which was mistaken for a main pulmonary trunk, originated from the left side of the truncus and divided into the upper and lower lobe arteries. The operation was uneventful and the child did well. Ventricular fibrillation occurred on the fourth

Table 2 *Truncus arteriosus in infancy — group 2*

Age	*Weight at operation (kg)*	*Origin of pulmonary arteries*	*Comment*
5 d	3·8	Pulmonary trunk	Death: moribund on admission
8 d	3·4	Pulmonary trunk	Death on table: intramyocardial injection of contrast material
17 d	3·1	Separate	Death after 1 d
28 d	2·4	Widely separate at different level	Well at 15 m
2 m	3·5	Pulmonary trunk	Well at 2 y
2 m	3·5	Pulmonary trunk	Recovering at 1 m
3 m	3·7	Pulmonary trunk	Well
5 m	3·9	Pulmonary trunk	Well at 16 m
5 m	3·9	Interrupted LPA originated from persistent ductus arteriosus	Death after 4 d: persistent ductus arteriosus not recognised
6 m	4·7	Pulmonary trunk	Well at 3 y
8 m	5·7	Separate	Well at 3 m
9 m	6·0	Separate	Death on table: grade III pulmonary vascular obstructive disease

d, day; m, month; y, year; LPA, left pulmonary artery.

postoperative day and was resistant to treatment. At necropsy, the true situation became apparent. The interrupted left pulmonary artery arose from a persistent ductus arteriosus and not from the right pulmonary artery.

The last child, the oldest in our series, had an uneventful repair. Ventricular fibrillation occurred without warning about 30 minutes after discontinuation of cardiopulmonary bypass and all resuscitative measures were unsuccessful. Histological examination of the lungs showed grade III pulmonary vascular obstructive disease (Heath and Edwards, 1958).

GROUP 3: EARLY ELECTIVE REPAIR FOR INCREASING PULMONARY ARTERIOLAR RESISTANCE

One patient with a raised pulmonary arteriolar resistance was referred for correction at the age of 11 months. His calculated pulmonary arteriolar resistance was 10 units m^2 BSA and arterial oxygen saturation was only 80 per cent breathing air. In an older child this would suggest an inoperable condition. Because he was only 11 months old, and after much discussion, we decided to offer him a corrective procedure. The operation was uneventful but the child died 28 hours later. Histology showed grade 3 pulmonary vascular obstructive disease.

Surgical considerations

(a) TECHNIQUE OF PERFUSION

We do not believe that it is important whether cardiopulmonary bypass or a technique of deep hypothermia and circulatory arrest is used, and indeed we often combine the two techniques. Older and larger children (over about 6 months of age and 5 kg) usually undergo operation using cardiopulmonary bypass with core cooling and one or two periods of low flow, sometimes including a short period of circulatory arrest at a low temperature. Two venous cannulae are inserted and the standard technique of cardiopulmonary bypass is employed.

In small sick infants we prefer to use surface cooling after the arterial monitoring line is inserted. The chest is opened when the nasopharyngeal temperature is lowered to 26 to 28 °C. The infant is connected to the heart/lung machine using a thin walled metal cannula placed in the aorta above the origin of the pulmonary arteries and one venous cannula in the right atrial appendage. The pulmonary arteries are snared or clamped to avoid overperfusion of the lungs. Using cardiopulmonary bypass, the nasopharyngeal temperature is lowered to 19 °C and the circulation stopped.

(b) OPERATIVE TECHNIQUE

The operative technique follows the principles outlined by McGoon and colleagues (1968). The aorta is cross-clamped, the root of the aorta perfused with cardioplegic solution, and then the pulmonary artery is detached from the aorta. Care should be taken when detaching the lower part of the pulmonary artery in infants as the origin of the pulmonary trunk may be close to a coronary artery orifice (Bharati *et al.*, 1974) (Fig. 1). An unusual problem was presented by an infant whose pulmonary arteries originated separately from the truncus at different levels. The origin of the right pulmonary artery was so high that it would have been difficult to cannulate the aorta above its origin (Fig. 2). The cannula was therefore placed

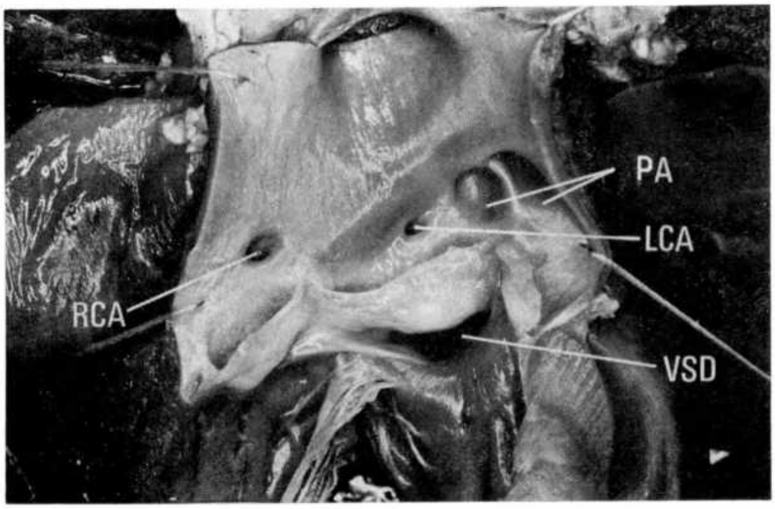


Fig. 1 *Ostium of the left coronary artery (LCA) is situated very close to the origin of the pulmonary arteries (PA). Ventricular septal defect (VSD) and right coronary artery ostium (RCA) are seen.*

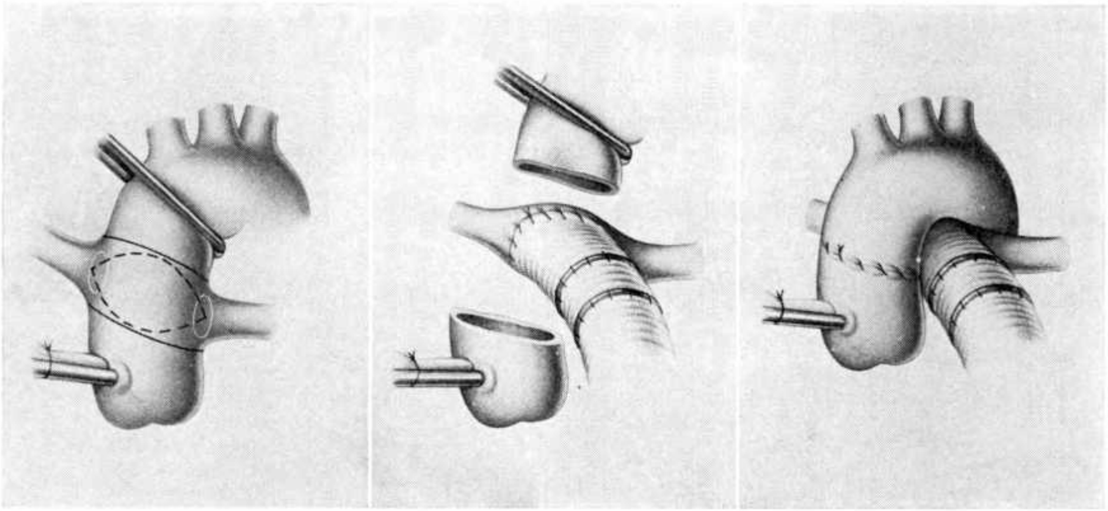


Fig. 2 (*a*) *The arterial cannula is placed between the truncal valve and the origin of the right pulmonary artery. Continuous lines indicate an oblique excision of a segment of the truncus including the origin of both pulmonary arteries. Dotted line shows the opening in the anterior wall which will be used for the anastomosis with the conduit.* (*b*) *Anastomosis between the excluded segment of the truncus and the valved conduit is completed. Division of the aorta facilitates access to the anastomosis.* (*c*) *Aortic continuity is re-established by end-to-end anastomosis. Air is evacuated from the aorta and aortic clamp released.*

between the truncal valve and the origin of this pulmonary artery. Under circulatory arrest, the truncus was transected above and below the origins of the pulmonary arteries and a cuff of the wall opened for the anastomosis with the conduit. Aortic continuity was re-established by an end-to-end anastomosis (Fig. 2).

The ventriculotomy is vertical pointing towards the pulmonary artery. The ventricular septal defect is closed with a generous patch of Dacron velour. The patch is brought up to the anterior right ventricular wall to provide a large ventricular outflow for the aorta (Fig. 3). It also serves to reinforce the attachment of the conduit to the right ventricle later. An extracardiac valved conduit is then used to establish continuity between the right ventricle and pulmonary artery. The anastomosis of the conduit to the pulmonary artery is performed using a continuous stitch of 5-0 Prolene. When this anastomosis has been completed, the foramen ovale is closed through the right atrium. If the operation is being performed using circulatory arrest with one venous cannula, it is possible to place two venous cannulae once the ventricular septal defect has been closed. The aortic clamp can then be removed and the patient completely rewarmed while the conduit is being anastomosed to the right ventricle. Time is thus saved and when the right atrium is closed and the anastomosis of the conduit to the right ventricle completed, perfusion can be terminated.

There are a few other technical points which should perhaps be emphasised. The conduit is not trimmed too short, so as to allow for growth of the patient. It is cut obliquely at the ventricular end to achieve a wide opening without a gradient (Fig. 4). We routinely resect the thymus to make more room for the conduit and also open the pericardium and pleura widely behind the heart. The heart then rotates to the left and allows the conduit to move away from the midline. Compression of the conduit by the sternum is thus avoided.

Perioperative care

Intensive care is required throughout all stages of treatment, that is before, during, and after operation. It does not differ from the care used for other ill infants with congenital heart defects. Intermittent positive pressure ventilation is used for at least 24 hours after operation and weaning from the ventilator is aided by using constant positive airway pressure with spontaneous breathing.

Discussion

The results of early 'correction' of persistent truncus arteriosus are encouraging. After initial successful case reports (Girinath, 1973; Kirklin,

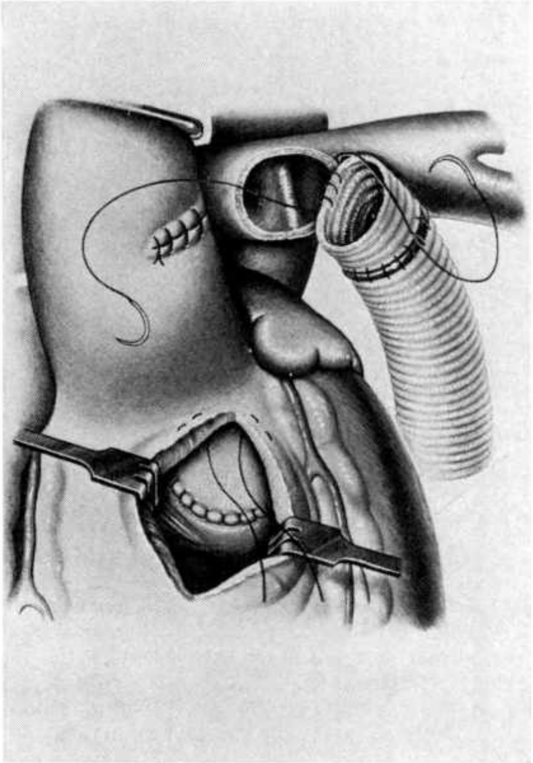


Fig. 3 *Closure of the ventricular septal defect. The patch is brought up to the anterior right ventricular wall. This creates a large outflow from the left ventricle to the aorta and the patch can be used to anchor the posterior part of the conduit to the right ventricle. Anastomosis of the conduit with the pulmonary artery is started.*

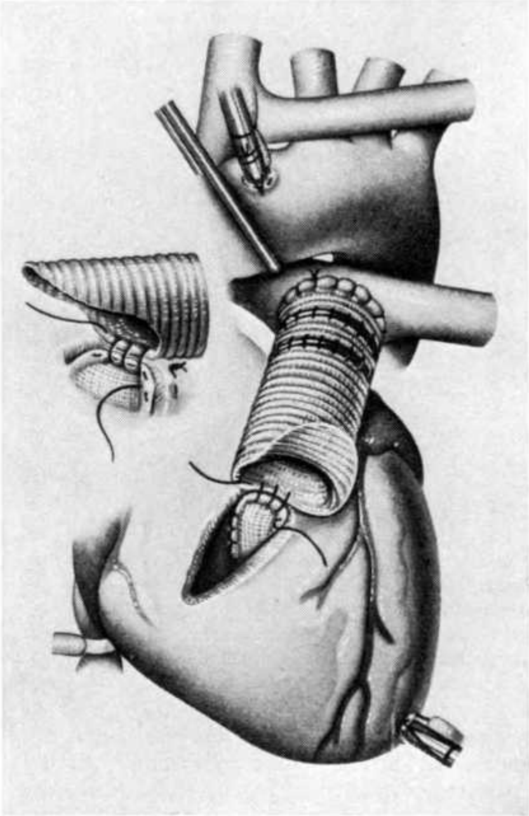


Fig. 4 *The conduit is trimmed obliquely at the ventricular end (see insert) to achieve a wide anastomosis. The anastomosis between the conduit and the right ventricle is done using 4-0 Prolene.*

1973; Singh *et al.*, 1975; Sullivan *et al.*, 1976), Stanger and colleagues (1977) reported a series of 21 infants with a remarkable result. Eighteen out of 23 infants (79%) survived the operation. Persistent truncus arteriosus is sufficiently uncommon for it to be impossible with any accuracy to compare the alternative management policies of (a) medical treatment in infancy followed by corrective surgery at the age of 5 years, (b) banding in infancy followed by debanding and corrective surgery later, and (c) primary correction in infancy. It is nevertheless instructive to ask, on the basis of such information as is available, how many patients out of 100 can be expected to be alive and well at 9 to 10 years of age with each of these management policies. The rough comparison in Table 3 is based on the following assumptions:

(i) 20 per cent of all infants with persistent truncus arteriosus survive the first year of life on medical treatment. The actual figures quoted are 0 (Marcelletti *et al.*, 1976), 15 per cent (Keith *et al.*, 1967), and 30 per cent (Nadas and Fyler, 1972).

(ii) The immediate mortality of banding of the pulmonary artery is 60 per cent. This is based on the figures of 56 per cent reported by Poirier *et al.* (1975) and 73 per cent by Singh *et al.* (1975).

(iii) 10 per cent of all patients who have had pulmonary artery banding in infancy are inoperable at 5 years. The figures reported by McFaul *et al.* (1976) were 1/22 (4·5%) for patients with two pulmonary arteries and 3/5 (60%) for patients with one pulmonary artery.

(iv) The immediate mortality for correction of truncus arteriosus after pulmonary artery banding is 11 per cent. Parker *et al.* (1975) reported an overall mortality of 20 per cent, but a 6 per cent mortality in a group of 17 children operated more recently.

(v) Of those patients who survive infancy, only half

Table 3 *Comparison of three management policies for patients with persistent truncus arteriosus*

Primary correction at 5 years		*Pulmonary artery banding in infancy; debanding and correction at 5 years*		*Primary correction in infancy and conduit replacement at 5 to 8 years**	
Born	100	Born	100	Born	100
Die < 1 year	80	Die at banding	60	Die at correction	40
Inoperable at 5 years	10	Inoperable at 5 years	4	Die at conduit replacement	2
Die at correction	1	Die at correction	6		
Alive and well at 9 years	9		30		58

*Deaths in infancy without operation are not included.

are suitable candidates for elective surgery at the age of 5 years. Of 70 patients investigated since 1967 at the Mayo Clinic, 40 were regarded as operable (Mair *et al.*, 1974), though several of these would not be deemed operable by current criteria.

(vi) The immediate mortality of surgical correction in infancy is 40 per cent. This is based upon 5/23 (Stanger *et al.*, 1977), 5/7 (Appelbaum *et al.*, 1976), and 6/13 in this series.

(vii) The immediate mortality of conduit replacement in childhood after primary 'correction' in infancy is 3 per cent. This is derived from the mortality for replacement of obstructed conduits of 0/17 in older children (0%) (Moodie *et al.*, 1976).

This analysis does not include late mortality after primary correction in later childhood, which has been reported and which is particularly common in patients with pre-existing pulmonary vascular disease (Marcelletti *et al.*, 1977). However, the late mortality after correction in infancy is not yet known. As is clear from this report, some infants are so sick that they do not even reach the operating table alive. These infants appear in Table 3 under the heading of 'Primary correction at 5 years' as deaths under 1 year, but not under the headings of 'Banding in infancy' and 'Correction in infancy.' Even so, the difference in overall survival between medical and surgical treatment in infancy is so great as to rule out medical treatment alone in all but the few cases who respond rapidly to a moderate antifailure regimen.

Table 4 *Valved conduit*

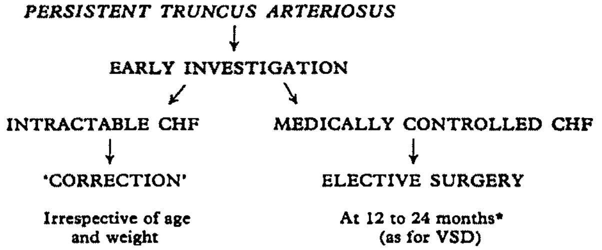
	For	*Against*
Homograft:	Cheap	Irradiated and frozen calcify
	Larger size fits Easier distal anastomosis	Availability
Heterograft:	Availability Quality control	Expensive Bulky in infants Gradients in small sizes

Accepting that surgical treatment is inevitable in patients in intractable heart failure, the difference between the policy of the two-stage correction and early primary correction (Table 3) is remarkable. Almost twice as many children can be expected to be alive and well using the latter approach. With increased experience, further reduction of operative mortality of early repair can be expected.

The type of valved conduit to be used is still open to discussion. Both homografts and heterografts have advantages and disadvantages (Table 4). Late complications, namely severe calcification and stenosis of the homograft conduit (Moodie *et al.*, 1976), led to the development of alternative materials. At the present time, a Dacron conduit containing a porcine valve is favoured by most surgeons. It is, however, probable that the complications of aortic homografts result from the technique of sterilisation and preservation rather than the properties of the homograft itself. Those which were irradiated and deep-frozen showed a high incidence of obstruction, but this was considerably greater for patients with complex transpositions (22%) than for patients with truncus arteriosus (3%) (Moodie *et al.*, 1976). Homografts preserved fresh in an antibiotic solution functioned well up to 9 years in patients operated upon by Ross (Moore *et al.*, 1976). We believe that the aortic homograft extended towards the right ventricle with a woven Dacron tube is the most suitable conduit particularly in infancy. We find it easier to suture the homograft to the small pulmonary artery in an infant, and also we can fit in a larger homograft than the more rigid 'Hancock' heterograft. Using an 18 to 22 mm homograft in infants, it is conceivable that replacement may not be necessary in the future.

The optimal timing of early elective repair is another unsolved problem. There are no difficulties in patients from groups 1 and 2 who were either desperately ill or in heart failure that was completely refractory to medical treatment. An urgent or semi-urgent operation is indicated, as any longer delay could be detrimental (group 1). The question remains as to when one should operate on patients

Table 5



*This age may need revision subsequent to further experience.
CHF, congestive heart failure; VSD, ventricular septal defect.

whose heart failure is controlled medically, but who have systemic pressure in the pulmonary arteries and are, therefore, at risk of early development of pulmonary vascular obstructive disease. It is certain that the age of 5 years suggested earlier (Marcelletti *et al.*, 1977) is far too late. Though the risk of correction for patients with low pulmonary vascular resistance will be very low at this age, too many patients will be inoperable by that time. One possible approach is to follow the criteria outlined for infants with ventricular septal defect by Blackstone *et al.* (1976). The initial operative mortality, late risk, and survival with normal or near normal pulmonary artery pressure should be taken into consideration. Stanger and colleagues (1977) recommended elective correction before the age of 6 months because of their observation of severe pulmonary vascular obstructive disease in patients aged 6 to 12 months. In their series, the mortality rate was 13 per cent (2 out of 15) under 6 months of age, and 37 per cent (3 out of 8) in the 6 to 12 month age group. In the latter group, pulmonary vascular obstructive disease was a significant factor. Our present policy (Table 5) is to correct asymptomatic patients between the age of 1 and 2 years, but we are constantly reviewing our experience and accept that we might have to alter this policy and operate earlier.

In conclusion, we think that infants with persistent truncus arteriosus and additional complex intracardiac anomalies and/or truncal valve regurgitation are likely to be at a very high risk irrespective of the type of treatment offered. Those who present with 'uncomplicated' persistent truncus arteriosus are most likely to benefit from the policy of early repair. It is important in determining a policy for the treatment of infants with persistent truncus arteriosus that one considers *all* patients born with this anomaly and not only those admitted for operation. Furthermore, the object of treatment is far more than merely to achieve survival. Our aim should be normally active children with a normal pulmonary artery pressure and no residual defect.

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Noninvasive cardiovascular findings in familial amyloid polyneuropathy

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SUMMARY The cardiovascular system was examined in 19 cases of familial amyloid polyneuropathy. In a group of patients with neurological involvement, various cardiac abnormalities were common, including orthostatic hypotension, prominent apex cardiographic A waves, abnormal apical systolic waves (bulges), systolic murmurs, mid-systolic clicks, QS waves, atrioventricular block, left bundle-branch block, and abnormalities of ejection time and pre-ejection period. Though there was one case with pronounced cardiac abnormality despite a normal neurological state, and though cardiovascular symptoms appeared later than neurological symptoms, the degree of cardiac involvement generally paralleled the severity of the neurological disorder.

Familial amyloid polyneuropathy initially involves the peripheral and autonomic nervous systems and later affects the cardiovascular system. Little is known about the cardiovascular functional effects of the disease, apart from the electrocardiographic abnormalities, and there has been no precise comparison between cardiac and neurological findings in this disease. Therefore, we studied several families with this disorder in Arao City, Kumamoto, where there is a very large incidence of this illness, in order to elucidate the type and severity of associated cardiac dysfunction using noninvasive methods.

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Subjects

We studied 12 cases, 7 men and 5 women, of familial amyloid polyneuropathy with neurological symptoms (the affected group), and 7 cases, 2 men and 5 women, without neurological symptoms (the non-affected group) (Table 1).

The average age of the affected group was 34·3 years. The duration of the disease ranged from 1 month to 17 years. On the basis of results of peripheral nerve function tests (measurements of motor and sensory nerve conduction velocities of ulnar, median, and peroneal nerves using Medelec MS6-1 Electromyograph) there were 7 cases showing no response to electric stimuli or a significant delay in

Table 1 *Peripheral nerve function tests in 12 patients with abnormal neurological findings (the affected group)*

	Age (y)	*Sex*	*Age at onset (y)*	*Duration (y)*	*Ulnar MCV (< 4·0 ms, 49 m/s)**	*Median SCV (< 3·2 ms, 62 m/s)**	*Peroneal MCV (< 7·0 ms, 43 m/s)**
1	47	M	30	17	(5·4, 23·6)	NR	NR
2	49	F	40	9	(7·4, 64·5)	(2·6, 55·6)	NR
3	41	F	33	8	(4·7, 44·7)	NR	NR
4	37	M	31	6	(4·7, 49·0)	(2·8, NR)	NR
5	25	M	19	6	(4·3, 63·2)	NR	NR
6	34	F	29	5	(2·5, 50·0)	(2·8, 59·7)	(6·9, 43·1)
7	34	M	30	4	(6·0, 40·2)	(4·5, 47·9)	NR
8	29	F	25	4	(3·3, 61·8)	(2·8, 67·7)	(4·0, 44·6)
9	29	M	27	2	(3·3, 58·5)	(0·6, 38·1)	(5·1, 40·5)
10	27	M	26	1	(2·4, 47·1)	(2·5, 61·4)	(5·9, 42·9)
11	31	F	31	2/12	(2·6, 63·4)	(2·3, 64·7)	(7·1, 52·6)
12	31	M	31	1/12	(3·6, 63·8)	(2·9, 61·1)	(6·0, 41·9)
Mean	34·5		29·3	5·2	(4·3 52·5)	(2·6 57·0)	(5·8 43·3)
± 1 SD	± 7·7		± 5·0	± 4·7	(± 1·6, ± 12·5)	(± 1·0, ± 9·7)	(± 1·2, ± 4·3)

MCV, motor conduction velocity; SCV, sensory conduction velocity; * normal values (latency, minimum velocity); NR, no response to the nerve stimulations.

Table 2 *Cardiovascular symptoms and physical signs in 2 groups of patients with familial amyloid polyneuropathy (FAP)*

		Affected		*Non-affected*
		All *12*	*Severe* *7*	*7*
(1) Symptom	Arrhythmia	4	4*	0
	Syncope	2	2	0
(2) Physical examination				
Blood pressure	Orthostatic hypotension	4	4*	0
Pulses	Arrhythmia	7	6*	1
Cardiac impulse	Abnormal systolic wave	6	5	0†
(apex cardiogram)	Large 'A'	4	4*	3
Cardiac auscultation	Systolic murmur	6	5	3
(phonocardiogram)	Systolic click	6	3	0†
	Gallop rhythm	3	3	0

* Statistically significant difference between the severe and mild subgroups.
† Statistically significant difference between the affected and the non-affected groups.

nerve conduction velocity. These cases were designated the severe group.

The average age of the non-affected group was 33·9 years.

Method

Each subject underwent the following: (1) careful historical review of symptoms related to the cardiovascular system, (2) physical examination of the cardiovascular system, (3) standard 12-lead electrocardiogram, (4) polygraphic recordings by our standard method (Sawayama *et al.*, 1973), using simultaneous phonocardiogram, apex cardiogram, carotid arterial pulse, and jugular venous pulse. In addition, measurements were made of the left ventricular systolic time intervals (LVSTI) [total systolic phase (Q-II), ejection time (ET), pre-ejection period (PEP) and ET/PEP ratio] (Sawayama *et al.*, 1973). The blood pressure was measured in the supine position and after 3 minutes in the sitting position.

Table 3 *Electrocardiogram and polygraphic recordings in 2 groups of patients with familial amyloid polyneuropathy*

	Affected		*Non-affected*
	All *12*	*Severe* *7*	*7*
(3) Electrocardiogram			
QS pattern	4	3	1
Sinoatrial block	1	1	0
AV block	6	5	1
complete	1	1	0
incomplete	5	4	1
BB block (left)	6 (5)	6 (5)*	0†
Extrasystole	2	2	1
ST-T change	5	2	1
Low voltage (limb)	0	0	1
Left ventricular hypertrophy	2	0	2
(4) Left ventricular systolic time intervals			
Abnormal ET and PEP	7	5	0†

AV, atrioventricular; BB, bundle-branch; ET, ejection time; PEP, pre-ejection period.
* Statistically significant difference between severe and mild subgroups.
† Statistically significant difference between the affected and the non-affected groups.

Results

Tables 2 and 3 list the results of all observations, and provide indications of statistical significance.

In the affected group the duration of subjective cardiovascular symptoms was 0 to 4 years, which was significantly shorter than that of the neurological symptoms. The main cardiovascular abnormalities were arrhythmias, syncopal attacks, and orthostatic hypotension. The apex cardiogram disclosed abnormal systolic waves (bulges) and prominent A wave, while the phonocardiogram showed significant systolic murmurs, mid-systolic clicks, and gallop rhythms. Such abnormalities were especially obvious in the neurologically severe group.

In contrast, in the non-affected group, arrhythmias, prominent A wave, and systolic murmurs were noted only in the patients with diabetes mellitus and hypertension.

Fig. 1 shows one patient from the affected group with an abnormal systolic bulge and mid-systolic click.

The electrocardiograms of the affected group showed infarction-like QS patterns, sinoatrial blocks, atrioventricular blocks, and left bundle-branch blocks. These abnormalities were more frequent in the neurologically severe group (Table 3). Significant prolongations of pre-ejection period (PEP) and significant reductions of ET/PEP were also more predominant in the severe group.

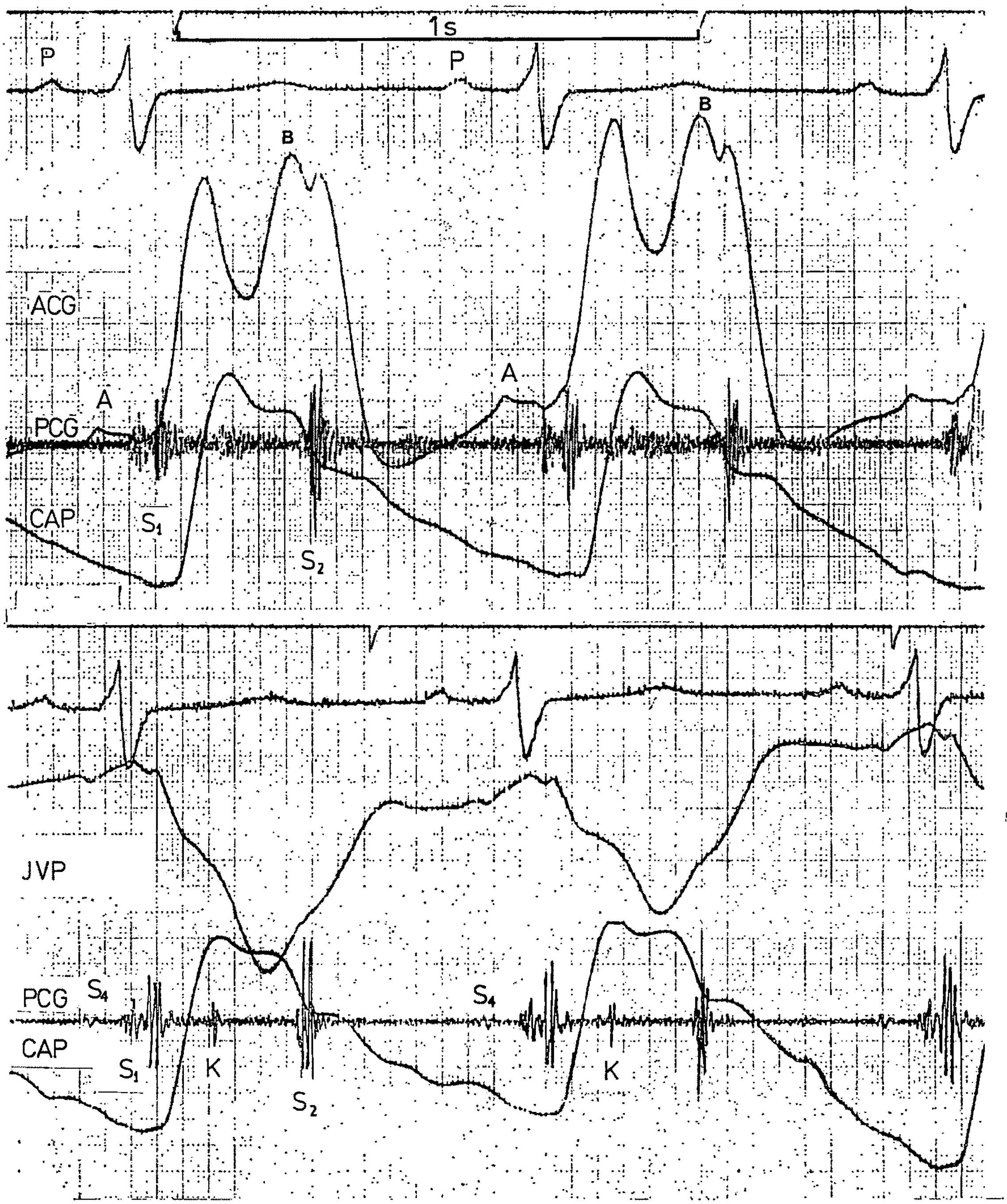

Fig. 1 *Case 1 in the affected group shows an abnormal systolic wave with late systolic bulge (B) in the apex cardiogram and a mid-systolic click (K) on phonocardiogram. ACG, apex cardiogram; CAP, carotid arterial pulse; JVP, jugular venous pulse; PCG, phonocardiogram.*

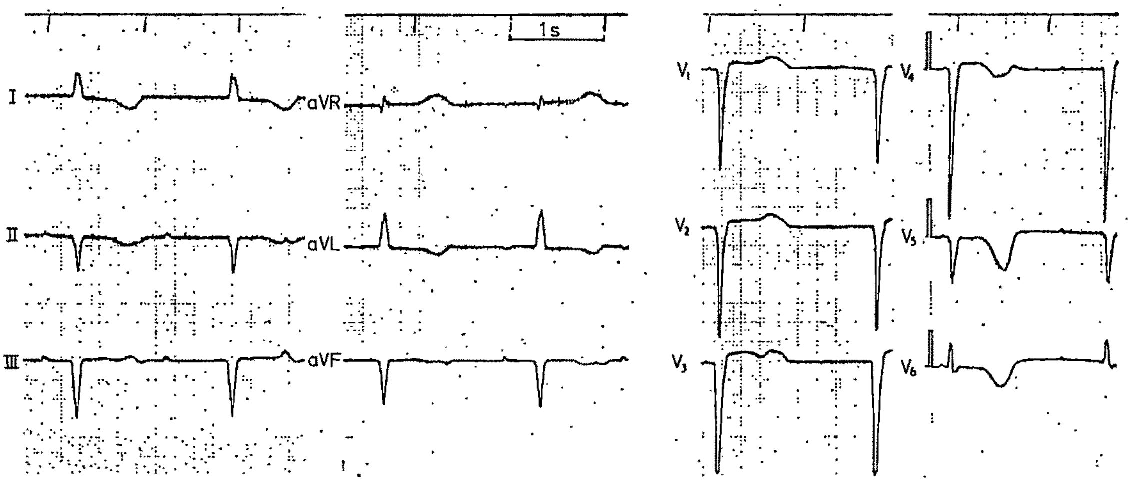

Fig. 2 *Case 2 in the affected group shows complete atrioventricular block, a QS pattern in II, III, aVF, V1-5, left axis deviation, left bundle-branch block, and distinct ST-T changes.*

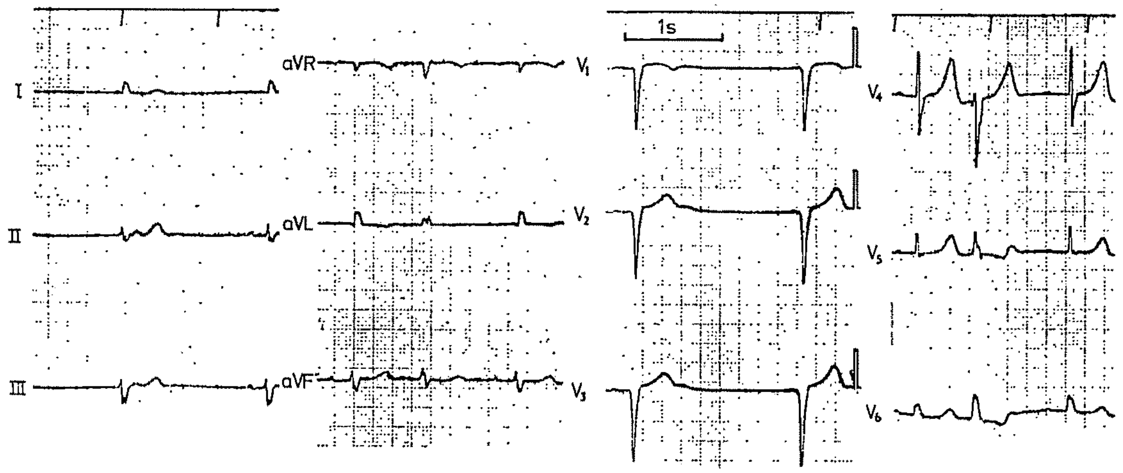

Fig. 3 *Case 3 in the affected group reveals sinoatrial block, a ventricular premature beat, a QS pattern in V1-3, left axis deviation, and left bundle-branch block.*

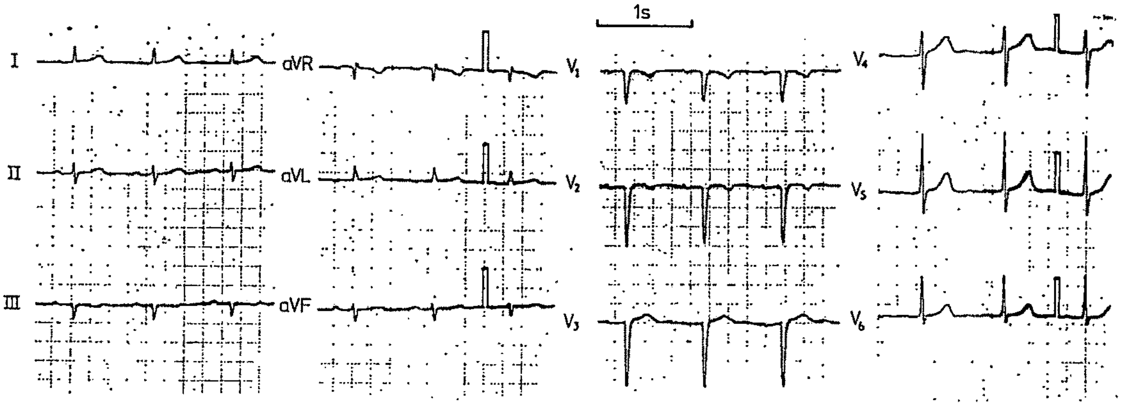

Fig. 4 *Case 5 in the non-affected group shows first degree atrioventricular block, low voltage in limb leads, left axis deviation, and a QS pattern in V1-3.*

The electrocardiograms of the non-affected group (with the exception of those cases having diabetes mellitus and hypertension) were abnormal in only one individual. In the non-affected group the left ventricular systolic time interval was normal.

Representative electrocardiographic abnormalities are illustrated in Figs 2 to 4.

Discussion

Cardiac involvement has been variably emphasised in previous reports of familial amyloid polyneuropathy. Frederiksen *et al.* (1962) found that congestive heart failure was often present when neurological symptoms were minimal. In the 3 cases reported by Allenworth *et al.* (1969), atrial standstill was noted but heart failure was not evident. Recently, Coelho and Pimentel (1961) in Portugal reported 34 cases of familial amyloid neuropathy of a special type. These cases showed distinct neuropathy but no cardiac symptoms. There were no pronounced changes in heart sounds, and all patients were in sinus rhythm. Only 20 of the cases showed abnormalities in the electrocardiogram, including premature beats, right and left ventricular hypertrophy, incomplete atrioventricular block, bundle-branch block, and non-specific T wave abnormalities. In the 4 cases with familial neuropathy reported by Buja *et al.* (1970), 1 had heart failure while 3 showed low voltage in the electrocardiogram.

These and other previous reports have suggested that various familial groups with amyloidosis may present quite different clinical syndromes, depending on the predilection for amyloid deposition in the nervous, cardiovascular, or renal systems, or in the conduction system vs. the general musculature of the heart. A similarity has been reported, in this regard, between the cases with familial amyloid neuropathy in Portugal and those in Japan (Andrade *et al.*, 1970). However, in the Japanese cases, the degree of cardiac dysfunction closely paralleled the severity of the neurological disorder, and a wide variety of electrocardiographic abnormalities were encountered, including infarction patterns, sinoatrial and atrioventricular conduction disturbances, left bundle-branch block, tachyarrhythmias, and non-specific ST-T abnormalities. Two of the patients with conduction disturbances (1 sinoatrial and 1 atrioventricular block) required permanent pacemakers because of syncopal attacks. Orthostatic hypotension was associated with severe cardiac dysfunction in 4 of our cases, though Buja *et al.* (1970) have pointed out that this relation is not consistent.

We have not found a full report of polygraphic findings in familial amyloid neuropathy. In our cases, an abnormal systolic wave was found in the apex cardiogram in 6 of 12 cases of the affected group (in 5 of the 7 severe cases). This abnormality has previously been reported predominantly in patients with ischaemic heart disease and cardiomyopathy (Benchimol, 1977). A prominent systolic murmur was recorded in 4 phonocardiograms and a mid-systolic click in 6 tracings. These findings may be related to papillary muscle dysfunction (Barlow *et al.*, 1968) because it is pertinent that half of the patients with extensive amyloid deposits in papillary muscles at necropsy had apical systolic murmurs (Buja *et al.*, 1970).

The left ventricular systolic time interval was abnormal in 8 of the 12 cases of our affected group. These abnormalities may have been, partly, the result of conduction abnormalities, but they strongly suggested primary myocardial involvement in view of their usually close relation to ventricular performance (Weissler *et al.*, 1968), and the frequently abnormal values found in other types of cardiomyopathy (Benchimol, 1977).

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Association of secundum atrial septal defect and atrioventricular nodal dysfunction

A genetically transmitted syndrome

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SUMMARY Secundum atrial septal defect may occasionally be transmitted as an autosomal dominant trait. Patients with this entity often show evidence of conduction system abnormalities by electrocardiogram. To define the nature of the conduction system disease in such patients, we studied a family in which 5 closely related members in 3 generations had the combination of atrial septal defect, syncope, and first and/or second degree atrioventricular (AV) block by electrocardiogram. Of these 5 patients, 3 had required permanent pacing. Three other relatives without syncope also had conduction abnormalities, including 1 patient with atrial septal defect. Of the 8 family members, 3 were studied with His bundle electrocardiography. Two of these 3 patients had syncope preceding operative closure of an atrial septal defect and one had no history of syncope or evidence of an atrial septal defect; all 3 had first degree AV block. Intracardiac electrophysiological study showed that each patient had a long AH time (which decreased with atropine), normal HV time, and prolonged AV nodal refractory periods. Thus, both secundum atrial septal defect and intrinsic AV nodal disease may be transmitted as autosomal dominant traits (probably as manifestations of a single mutant gene), and may occur together or separately in members of the same family.

The association of secundum atrial septal defect with prolonged atrioventricular (AV) conduction, which is transmitted as an autosomal dominant trait in certain families, represents a recognised clinical syndrome (Kahler *et al.*, 1966; Amarasingham and Fleming, 1967; Bizarro *et al.*, 1970; Björnstad, 1974; Emanuel *et al.*, 1975; Pease *et al.*, 1976). However, in all but one of these previous reports, evidence of abnormal AV conduction was obtained from the surface electrocardiogram only. Hence, the precise nature of the conduction system disease in such patients has not been defined. In the present report, we describe findings in a family in which secundum atrial septal defect was associated with a conduction disturbance localised in the AV node (as determined by His bundle electrocardiography) in several closely related relatives in 3 generations.

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Selection of patients

Members of the family were originally evaluated by physical examination and electrocardiogram, as described in an earlier report (Kahler *et al.*, 1966). The present study is concerned with recent observations made on 8 affected family members, including 2 patients not included in the earlier report. Each of these 8 patients had either a secundum atrial septal defect, electrocardiographic evidence of prolonged AV conduction, syncope, or various combinations of these findings. Each patient also had a consistently normal heart rate under basal conditions (more than 60 beats per minute in adult patients). The relevant portion of the pedigree is shown in Fig. 1.

Two other members of the family (C.L. and G.L.) who were noted to have cardiac abnormalities when the family was initially screened (Kahler *et al.*, 1966) were not available for this study. Both these patients

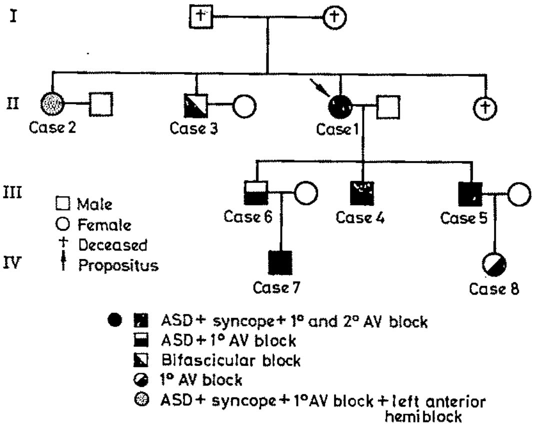

Fig. 1 *Family pedigree. Both parents and one sib of the propositus died of non-cardiac causes over the age of 60 years.*

were second cousins to cases 4, 5, and 6. C.L. was a 27-year-old man in whom a previous electrocardiogram showed complete right bundle-branch block (QRS 0·14 s), right axis deviation, and nonspecific ST segment and T wave changes. Cardiac catheterisation at age 15 years showed a normal heart without evidence of an intracardiac shunt. G.L. was a 24-year-old man who had a large atrial septal defect ($\dot{Q}p:\dot{Q}s = 2{\cdot}2$) that was operatively repaired at age 11 years. Previous electrocardiograms had been normal. Neither of these men had had syncope.

Methods

HAEMODYNAMIC STUDIES

Routine right heart catheterisation was performed in the postabsorptive state using local anaesthesia but no sedation in 2 adults (cases 1 and 5), and after sedation with pethidine, chlorpromazine, and promethazine in a child (case 8), aged 2 years. None of the 3 patients was taking a cardioactive agent at the time of the study. Pressure recordings and blood samples for oxygen analysis and shunt determination were obtained in the pulmonary artery, right ventricle, right atrium, and superior and inferior vena cava. Two of the 3 patients (cases 1 and 5) were studied several years after the operative closure of atrial septal defect.

HIS BUNDLE STUDIES

After completion of the haemodynamic study, a quadripolar electrode catheter was percutaneously introduced via either an antecubital or a femoral vein and advanced under fluoroscopic guidance to the lateral wall of the right atrium near its junction with the superior vena cava. The proximal pair of electrodes was used to record a high right atrial electrogram. The distal pair of electrodes was used to stimulate the atrium. A second quadripolar catheter was percutaneously introduced via the right femoral vein and was positioned across the tricuspid valve to obtain a His bundle electrogram using methods previously described (Scherlag *et al.*, 1969). In the 2 adult patients an additional bipolar electrode catheter was introduced percutaneously via a femoral vein and positioned in the apex of the right ventricle for the purpose of ventricular stimulation.

Intracardiac electrograms (high right atrium, low right atrium, His bundle, and right ventricle) were all recorded with filter settings at 40 and 500 Hz. Electrocardiographic leads I, II, III, and V1 (filtered at 0·1 and 200 Hz) and time lines at 10 and 100 ms were displayed on a multichannel oscilloscope and recorded on magnetic tape. The tracings were subsequently replayed and recorded on photographic paper at a speed of 150 mm per second. Refractory periods of the atrium, atrioventricular node, and right ventricle were determined by the extrastimulus method (Krayer *et al.*, 1951; Goldreyer and Bigger, 1969) during anterograde conduction using a programmed digital stimulator which delivered impulses of 1·5 ms duration at twice diastolic threshold. Each patient was paced at a constant rate to avoid the effect of changing cycle length on refractoriness. The atrium was driven at a basic cycle length and after every eighth driven beat a premature stimulus was introduced at progressively shorter intervals up to the point of atrial refractoriness. A similar procedure was used in stimulating the ventricle. Determination of retrograde AV nodal conduction time (VA) was attempted in the 2 adult patients tested, but complete retrograde VA block was present during ventricular pacing in each.

The AH interval was measured from the onset of the low atrial electrogram to the earliest onset of the His bundle deflection. The HV interval was measured from the initial His deflection to the earliest point of ventricular depolarisation on either a surface electrocardiographic lead or the intracardiac electrogram. The PA interval was measured from the onset of P wave to earliest onset of low right atrial activity. Atrial effective refractory period (A-ERP), AV node effective refractory period (AVN-ERP), and corrected sinus node recovery time (CSNRT) were measured using methods previously described (Akhtar *et al.*, 1975; Narula, 1975). Electrophysiological measurements were made in the basal state and again after intravenous administration of atropine (0·5 mg in each adult;

Table 1 *Clinical and electrocardiographic data in 8 affected members of family*

Case No.	*Present age*	*Sex*	*Haemodynamics*				*Electrocardiograms*		
			Syncopal spells	$\dot{Q}p:\dot{Q}s$	*RV S/D (mmHg)*	*ASD repair*	*PR interval (s)*	*QRS interval (s)*	*Other AV conduction abnormalities*
1	50	F	At age 23 and 34 only	1·7	25/3	Age 37 y (secundum; 2·5 cm diameter)	0·22	0·09	Wenckebach type 2° AV block; leftward QRS axis (−20°); Rsr′ in V1
2	68	F	Occasional	1·1	29/5	None	0·40	0·12	LAD (−100°)
3	62	M	None	No ASD	28/5	None	0·20	0·14	RBBB; LAD (−65°)
4	22	M	Several since age 2 years*; demand pacemaker inserted age 14 and no subsequent syncope	1·2	36/0	None	0·44	0·09	Wenckebach type 2° AV block
5	24	M	About 10 since age 10 years†; demand pacemaker inserted age 20 and no subsequent syncope	2·1	18/4	Age 20 y (secundum; 3 cm diameter)	0·28	0·10	2° (2:1) AV block‡; complete heart block§
6	27	M	None	3·0	37/10	Age 9 y (secundum; 2 cm diameter)	0·40	0·08	None
7	6	M	One at age 6 w and one at age 5 mth; demand pacemaker inserted age 5 mth and no subsequent syncope	2·2	60/8**	Age 4 y (secundum; 2 cm diameter)	0·21¶	0·07	Wenckebach type 2° AV block††; Rsr′ in V1
8	3	F	None	No ASD	28/8	None	0·18	0·05	Rsr′ in V1

* Clinically, spells were thought to be Adams-Stokes attacks, occurring during sleep and preceded by complaints of abdominal pain, nausea, malaise, and crying out; during episodes the patient would become apnoeic and cyanotic for 10 to 30 seconds with documented heart rate of 20 to 35 beats/minute.

† Clinically, spells were thought to be Adams-Stokes attacks; episodes were precipitated by straining at the toilet or noxious stimuli and consisted of brief losses of consciousness preceded by sweating, nausea, and bradycardia.

‡ During cardiac catheterisation, second degree AV block was induced by simultaneous administration of isoprenaline and Valsalva manoeuvre.

§ During cardiac catheterisation, complete heart block was induced by the administration of edrophonium (0·6 mg).

¶ Lengthened to 0·32 s while taking digitalis.

** Pulmonary arterial pressure of 30/10 mmHg with peak systolic right ventricular outflow gradient of 30 mmHg.

†† While taking digitalis.

Abbreviations: ASD, atrial septal defect; AV, atrioventricular; LAD, left axis deviation; $\dot{Q}p:\dot{Q}s$, pulmonary-to-systemic flow ratio; RV, right ventricular pressure; S/D, systolic/end-diastolic pressure.

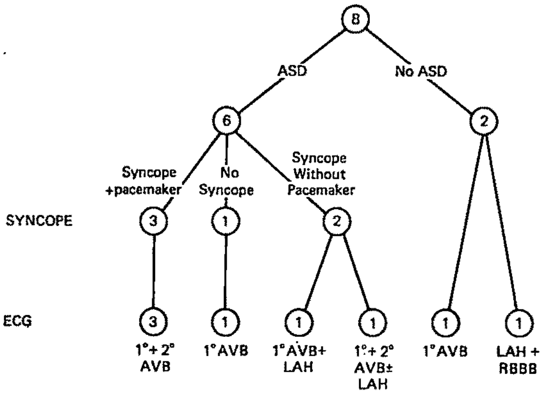

Fig. 2 *Diagram summarising salient clinical features of the eight affected members. AVB, atrioventricular block; LAH, left anterior hemiblock; RBBB, right bundle-branch block.*

0·1 mg in the child), and were compared with normal values obtained in adults (Dhingra *et al.*, 1973; Denes *et al.*, 1974; Akhtar *et al.*, 1975; Narula, 1975) or in children (Abella *et al.*, 1972; Anderson *et al.*, 1973; Levin *et al.*, 1977).

Results

CLINICAL FINDINGS

The clinical, haemodynamic, and electrocardiographic data are summarised in Table 1 and Fig. 2. Of the 8 affected family members, 6 had haemodynamic or operative evidence of a secundum atrial septal defect. The atrial septal defect was large and required operation in 4 patients (cases 1, 5, 6, and 7); in the other 2 patients (cases 2 and 4) the atrial septal defect was small ($\dot{Q}p:\dot{Q}s$ of 1·1 and 1·2, respectively, as determined by Krypton^{85} and dye

Table 2 *Electrophysiological data in 3 patients with secundum atrial septal defect*

Case no.	*Age (y)*	*Max. Pacing CL*	*PR (ms)*			*QRS (ms)*		*PA (ms)*
			Basal	*Max. pacing*	*Atropine*	*Basal*	*Max. pacing*	*Basal*
1	49	800	300	305	215	85	85	15
5	23	700	255	300	180	85	85	35
8	2	460	185	235	175	75	75	10
Normal for cases 1 and 5		—	120-190	—	—	80-110	—	15-45
Normal for case 8		—	120-150	—	—	40-90	—	10-40

Abbreviations: A-ERP, atrial effective refractory period; AH, atrium to His conduction; AVN-ERP, atrioventricular node effective refractory pe CL, cycle length; CSNRT, corrected sinus node refractory time; HV, His to ventricle conduction; Max., maximum; PA, measure of intra-atrial duction (interval from onset of P wave to earliest onset of low right atrial activity as recorded on His bundle electrocardiogram).

— data not available.

* also 2:1 atrioventricular nodal block (cycle length of 350 ms).

dilution curve analyses) and no operation was performed.

Cases 4, 5, and 7 with atrial septal defect experienced repeated episodes of syncope for which permanent demand right ventricular pacemakers had been inserted. None of these 3 patients has had a syncopal episode since insertion of the pacemaker (3, 5, and 7 years later, respectively). Two other patients with atrial septal defect have had syncopal attacks, but have not had pacemakers inserted; 1 (case 1) of these 2 patients had a history of 2 syncopal attacks, but none within the past 15 years, while the other patient (case 2) continues to have occasional episodes of syncope at age 68 years without serious consequences. One patient (case 6), who had a large atrial septal defect closed at operation, has remained asymptomatic.

Both of the patients without an atrial septal defect (cases 3 and 8) are asymptomatic. Each, however, has a conduction abnormality on surface electrocardiogram (first degree AV block in case 8 and bifascicular block in case 3).

ELECTROCARDIOGRAPHIC FINDINGS

Of the 8 patients, 7 showed consistent prolongation of the PR interval on the surface electrocardiogram. PR intervals ranged from 0·18 s in case 8, a 2-year-old infant (upper limit of normal 0·15 s), to 0·44 s. The remaining patient (case 3) had a borderline PR interval of 0·20 s. QRS duration was normal in 6 patients and prolonged ($\geqslant$ 0·12 s) in cases 2 and 3.

The precise mechanism of syncope in the 5 patients had not been defined by electrocardiography. In particular, complete heart block was not documented in these patients, except transiently in case 5 after administration of edrophonium. However, 2 of the patients (cases 1 and 4) with syncope had several documented periods of Wenckebach type second degree AV block; case 7 showed this conduction abnormality only while taking digitalis.

Three patients (cases 1, 2, and 3) have shown changes in their electrocardiograms over the past 10 years, with increasing leftward shift of the mean frontal plane QRS axis. In 2 (cases 2 and 3) of these patients the QRS axis ultimately exceeded −50° and in case 1 the QRS axis became −20°.

HIS BUNDLE ELECTROGRAMS

Data obtained from electrophysiological studies in the 3 patients were similar and consistent with the presence of proximal conduction system disease localised to the AV node. These data are summarised in Table 2 and shown in Fig. 3. The PR interval was prolonged under basal conditions in each patient. In addition, AH intervals and AV node effective refractory periods were prolonged in each patient under basal conditions. HV intervals were normal; block below the His bundle was not identified in any patient under basal conditions. Retrograde AV nodal conduction (VA) was not seen during ventricular stimulation. However, the exact location of retrograde AV nodal block was not identified since retrograde His potentials were not observed during AV dissociation. Split His potentials were not observed, thereby excluding the possibility of intra-Hisian block. In one patient (case 5) His bundle pacing resulted in 1:1 ventricular activation up to 200 beats per minute, with QRS complex morphology identical to that seen during sinus rhythm. In addition, atrial pacing resulted in AV nodal block at heart rates slower than 200 beats per minute, indicating that the conduction abnormality in this patient was in the AV node and not in the His-Purkinje system.

In each patient, with the administration of atropine, PR intervals decreased, AH intervals and AV node effective refractory periods shortened (but not to normal for subjects who had *not* received atropine), and HV intervals were unchanged. With

			HV (*ms*)		*AVN-ERP* (*ms*)		*A-ERP* (*ms*)		*CSNRT* (*ms*)	*Wenckebach* (*CL*)
al	*Max. pacing*	*Atropine*	*Basal*	*Max. pacing*	*Max. pacing*	*Atropine*	*Max. pacing*	*Atropine*	*Max. pacing*	
	265	175	40	40	780	430	230	220	640	750
	255	135	45	45	510	450	240	220	595	690
	190	130	35	35	370	320	260	260	—	445*
40	—	—	30-55	—	250-365	—	150-360	—	100-525	—
05	—	—	20-45	—	—	—	—	—	—	—

rapid atrial pacing, PR and AH intervals increased and HV interval did not change.

QRS duration was normal under basal conditions in each patient, and did not change during rapid atrial pacing, with extrastimuli during pacing, or with the administration of atropine. There was no other alteration in intraventricular conduction under these conditions, either on the surface electrocardiogram or on the His bundle electrogram which showed no anterograde infra-Hisian block. These findings suggest that, in the patients studied, functionally important disease of the distal conduction system was absent. Of interest, the corrected sinus node recovery time (Krayer *et al.*, 1951) was prolonged in both adult patients, suggesting the presence of sinus node dysfunction. However, PA times were normal indicating that there was no abnormality of intra-atrial conduction. In each of the 3 patients studied, right heart haemodynamics were normal and there was no evidence of an intracardiac shunt.

Discussion

The data in this report indicate that secundum atrial septal defect and intrinsic AV nodal disease may occur together or separately in members of the same family. The family we studied includes 5 closely related members in 3 generations with secundum atrial septal defect and syncope, as well as either first degree AV block, second degree AV block, or both, on electrocardiogram. It is, therefore, likely that in this particular family an autosomal dominant pattern of transmission for this syndrome exists.

Secundum atrial septal defect appears to have an increased prevalence in certain families (Carleton *et al.*, 1958; Zetterqvist, 1960; Campbell and Polani, 1961; Howitt, 1961; Weil and Allenstein, 1961; Zuckerman *et al.*, 1962; Johansson and Sievers, 1967; Nora *et al.*, 1967; Nora, 1968; Zetterqvist *et al.*, 1971; Libshitz and Barth, 1974; Nora and Nora, 1976). In these few families the genetic transmission appears to be most consistent with either an autosomal

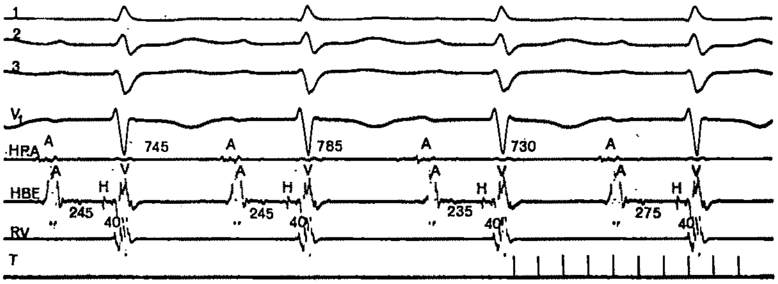

Fig. 3 *His bundle electrocardiogram in case 1. AH interval is prolonged (235-275 ms) and HV interval is normal (40 ms). The small negative deflection following the His potential is believed to be the right bundle-branch potential (right bundle-branch to ventricular deflection = 15 ms). HRA = high right atrial electrogram; HBE = His bundle electrogram; RV = right ventricular electrogram; A = atrial deflection; H = His bundle deflection; V = ventricular deflection; T = time lines (100 ms intervals). Cycle lengths (ms) are shown above HRA tracing.*

dominant (Zetterqvist, 1960; Campbell and Polani, 1961; Howitt, 1961; Zuckerman *et al.*, 1962; Johansson and Sievers, 1967; Zetterqvist *et al.*, 1971; Libshitz and Barth, 1974) or autosomal recessive (Carleton *et al.*, 1958; Campbell and Polani, 1961; Nora *et al.*, 1967) trait. However, Nora *et al.* (1967) have emphasised that multifactorial inheritance seems to account for the majority of cases of atrial septal defect. Nevertheless, in those particular families in which the pattern of inheritance seems most consistent with autosomal dominant transmission, secundum atrial septal defect may often coexist with AV conduction abnormalities, as seen on the surface electrocardiogram (Kahler *et al.*, 1966; Amarasingham and Fleming, 1967; Bizarro *et al.*, 1970; Björnstad, 1974; Emanuel *et al.*, 1975; Pease *et al.*, 1976). In these families the electrocardiographic conduction abnormality is most commonly first degree AV block, though second degree AV block of the Wenckebach type and complete heart block also occur.

Data obtained from our His bundle electrocardiograms provide evidence that the conduction system abnormality in the patients studied is localised primarily in the AV node. Cases 1 and 5 each of whom had atrial septal defect, first and/or second degree AV block, and syncope (case 5 required a permanent pacemaker) showed prolonged AH time and normal HV time. These findings are similar to those briefly described in a patient with secundum atrial septal defect, first degree AV block, and intermittent second degree AV block of the Wenckebach type (Pease *et al.*, 1976).

It is worth emphasising that the shortening of AH times and AV nodal refractory periods which followed the administration of atropine to our 3 patients who had electrophysiological studies showed only that vagal tone was present. Increased vagal tone, however, cannot be incriminated as the sole cause of the electrocardiographic and electrophysiological findings in our patients because each of the 8 patients studied showed consistently normal heart rates under basal conditions.

The finding on the electrocardiogram of left axis deviation and prolonged QRS duration in cases 2 and 3, and leftward progression of the QRS axis in case 1 suggest that the conduction disease is not localised entirely to the AV node in these patients. Nevertheless, all 3 patients studied with His bundle electrocardiograms (including case 1) showed normal HV time. Moreover, neither rapid atrial pacing, extrastimuli, nor atropine resulted in deterioration in distal conduction (QRS complexes and HV time were unchanged) or block below the His bundle. Hence, it appears that, in these patients, functionally important disease of the distal conduction system is not a part of this syndrome, a least at this time.

The mechanism of syncope in patients with atrial septal defect and intrinsic AV nodal disease is unclear. However, it is possible that such syncope is explained by potentiation of conduction delays resulting from transient increases in vagal tone. However, in previous descriptions of this syndrome syncope has been an uncommon manifestation.

Of interest, case 8 (daughter of case 5), who had first degree AV block but no atrial septal defect, showed abnormalities on the His bundle electrograms similar to those seen in cases 1 and 5. These findings suggest that the AV nodal disease present in this syndrome may be genetically transmitted independently of, as well as in association with, an atrial septal defect. However, we cannot exclude the possibility that incomplete genetic penetrance is responsible for this variable phenotypic expression of the syndrome. While it cannot be established from our study whether the AV nodal disease and atrial septal defect were transmitted on one or two gene loci, it seems most likely that a single locus is responsible and that these two abnormalities are therefore manifestations of a single mutant gene.

Although AV nodal disease was the predominant abnormality in our patients, both adult patients also had slightly prolonged sinus node recovery times, suggestive of a sinus node abnormality. Hence, we cannot exclude the possibility that syncope in our patients was the result, in part, of sinus node dysfunction. Furthermore, these observations suggest a close relation between sinoatrial and AV nodal development, and may be relevant to the reported presence of AV nodal disease in some patients with sick sinus syndrome (Narula, 1971).

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Nail haemorrhages

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SUMMARY Observations on the personnel in our laboratory, and two previously published studies make it clear that small nail haemorrhages are common and are not necessarily indicative of disease. Their site of origin and aetiology have not been studied and established. We investigated the incidence, site, and movement of such haemorrhages in one of us who is in good health and right-handed. The haemorrhages take place from capillaries in the centre of whorls of squamous epithelium beneath the deep soft nail plate. They develop at the line of separation of the nail plate from the nail bed and thus appear to be traumatic in origin. They were commoner in the first three fingers of both hands, that is in the digits most subjected to minor trauma in the subject studied. With the passage of time they move superficially and outwards to the nail margin. Histochemical studies of nail parings confirm that the linear discolorations are derived from blood. Their pathogenesis resembles that of 'black heel' in children. Nail haemorrhages are clearly not pathognomonic of subacute bacterial endocarditis and may occur in healthy subjects as the result of minor trauma. Nevertheless, recognition of this fact should not lead the clinician to ignore out of hand the presence of nail haemorrhages for in some instances they may still be supportive evidence of infective endocarditis, especially if they are frequent and numerous. Each case must be considered on its merits.

Splinter haemorrhages beneath the nails constitute a classical clinical sign which was originally associated with a diagnosis of subacute bacterial endocarditis over half a century ago by Horder (1920). He said: 'Twice in the past few months I have found a minute petechia, in the form of a vivid linear splash of red at the side of the bed of a finger-nail, in cases in which there were, as yet, no skin petechiae to be found, and in which the diagnosis of infective endocarditis was doubtful, but later established'. It is now generally accepted that such nail haemorrhages may form supportive evidence of infective endocarditis, especially when they are frequent and numerous.

However, it is also widely recognised that nail haemorrhages are not pathognomonic of subacute bacterial endocarditis. We became aware of this during an expedition to the Peruvian Andes in 1975 when we noted that many of the Quechua Indians living in the vicinity of Cerro de Pasco at an altitude of 4330 m above sea level had haemorrhages in their fingernails (Heath and Williams, 1977) (Fig. 1). Even more impressive were the haemorrhages that we found in the nails of highlanders suffering from Monge's disease (chronic mountain sickness), some of whom had as many as 10 haemorrhages scattered throughout the nail (Heath and Williams, 1977). We became further interested when we read the report of Drummond Rennie (1974) that on an expedition to Dhaulagiri, Nepal (8170 m), the sixth highest mountain in the world, he developed haemorrhages in his fingernails. This newfound interest in the fingernails led us to maintain a close observation on our own nails when we returned from Peru to Liverpool. It soon became clear that the propensity to develop haemorrhages in the nails was not confined to the descendants of the Incas or to high altitude climbers but was shared by lowlanders. Both of us who had been to the Andes had recurrent haemorrhages in the nails on return to Merseyside. When it subsequently transpired that the senior chief technician and a secretary in our department also had recurrent nail haemorrhages (Fig. 2), we thought it would be of interest to study their incidence and site of origin.

Methods of study

We studied the incidence, site of origin on the nail, and movement of haemorrhages in the finger and toenails in one of the authors (D.H.) from 1 January to 30 June 1977. All haemorrhages were photographed on the day of their appearance and subsequently at intervals of 5 days. A line diagram,

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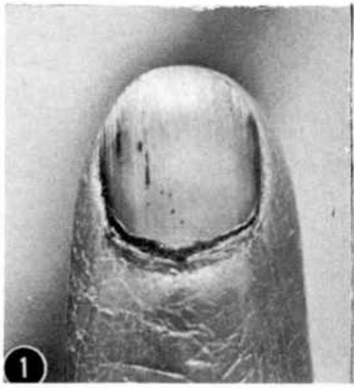
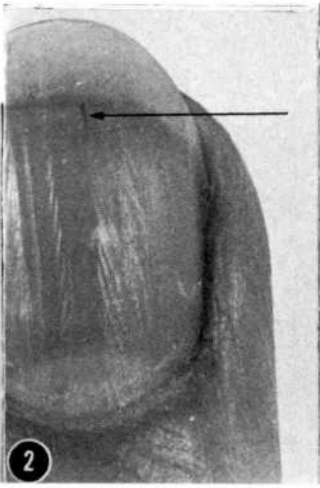




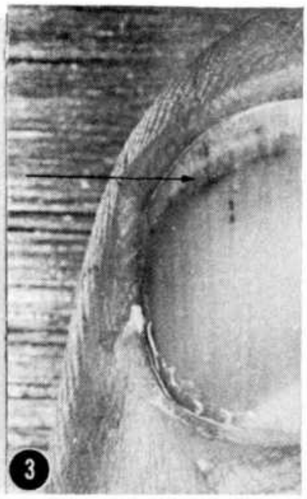


Fig. 1 *Nail haemorrhages in a Quechua Indian native to Cerro de Pasco at an altitude of 4330 m in the Peruvian Andes.* (×1·6.)

Fig. 2 *Nail haemorrhage in the third right finger in the right-handed 24-year-old secretary of one of the authors. The linear haemorrhage (arrow) occurs at the line of separation of nail plate from nail bed.* (×3·2.)

Fig. 3 *Linear haemorrhage in the right thumb nail of one of the authors (D.H.) on 22 April 1977. There is a row of nail haemorrhages at the line of separation of the nail plate from underlying nail bed (arrow).* (×3·2.)

at a magnification of ×4, was made from a life-sized photograph of each nail. A grid, with vertical and horizontal lines 2 mm apart, was drawn on this diagram. The composite diagram and grid were drawn on transparent film and superimposed over photographic prints of nails showing haemorrhages to facilitate measurements of their size, site, and movement.

When a haemorrhage had grown to the edge of the nail, the paring containing it was sectioned and stained, to confirm its nature and to determine its site of origin. To prepare satisfactory thin sections of nail it is necessary to use methacrylate-embedded material. The parings were dehydrated up to absolute alcohol by normal processing schedules and then left overnight in a solution of 2-hydroxyethyl-methacrylate, 2-butoxyethanol, and benzoyl peroxide. The nail was then cast in 42 parts of this mixture with 1 part of polyethylene glycol and NN dimethylaniline. Polymerisation occurred in 30 minutes and then blocks were trimmed with a hacksaw and attached to a wooden block with beeswax. Sections were cut on a base sledge microtome and the technique described allowed the production of sections some 2 to 4 μm in thickness. After being placed in an incubator at 60°C for at least one hour the sections were stained with haematoxylin and eosin, and with Van Gieson's stain.

The sections were also stained by the leuco-aniline blue technique which indicates the presence of peroxidase which is associated with erythrocytes. Aniline blue is reduced, and thus decolorised, with nascent hydrogen to leuco-aniline blue. When this comes into contact with extravasated erythrocytes their contained peroxidase catalyses the transfer of oxygen from added hydrogen peroxide to the leuco form of the dye. Hence its blue colour returns indicating the presence of altered blood.

Results

CLINICAL

The haemorrhages were linear or, less commonly, punctate (Fig. 3). The former measured some 1·0 × 0·25 mm while the latter were about 0·25 mm diameter. They did not develop at the root or throughout the nail but instead appeared in a line where the nail separates from the underlying nail bed (Fig. 3). With the passage of time the haemorrhages grew towards the nail edge, thus showing that they were within the substance of the nail and not petechiae. The nails were under observation for 182 days and moved at a rate of 0·14 to 0·19 mm

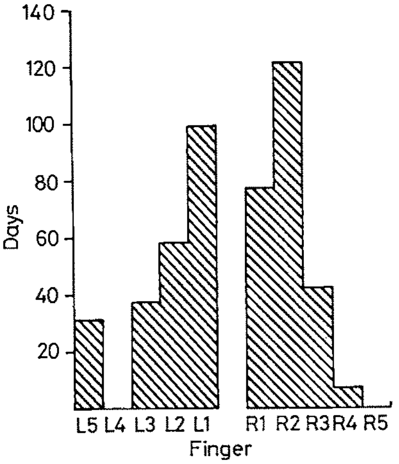


Fig. 4 *The number of days on which haemorrhages were found in the fingernails of one of the authors (D.H.) over a period of six months from 1 January 1977. Haemorrhages are seen to be commoner in the first three fingers of both hands and are somewhat more frequent in the right hand.*

per day. If large, the haemorrhages persisted as linear streaks and subsequently became available for histological study in nail parings. Not infrequently, however, they became paler and fragmented as they passed to the nail edge, and below we comment on the histological appearances associated with this change. They were frequent in the first three fingers of both hands but much less common in the fourth and fifth fingers (Fig. 4). They were rare in the toenails, occurring on only one occasion in the right big toe during the 6-month period of study (Fig. 5). The haemorrhages were somewhat commoner in the right hand (Fig. 4), the subject studied being right-handed.

HISTOCHEMICAL

The leuco-aniline blue technique confirmed that the brown linear streaks in the nails contained peroxidase and were thus consistent with being altered blood.

HISTOLOGICAL

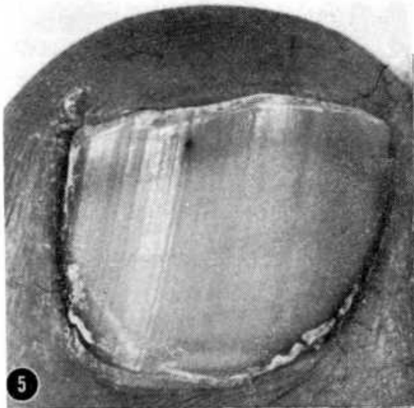
The thin sections of methacrylate-embedded nail parings revealed that the haemorrhages occurred deep in the nail plate where the undersurface of the nail separated from the nail bed. When methacrylate sections of nail are cut parallel to the surface one traverses at first the superficial hard nail plate (Fig. 6). Deeper sections in this plane reach the underlying softer nail plate (Fig. 7). Deeper sections still reveal the tips of upwardly projecting papillae of squamous cells (Fig. 8). It is at this level and in such whorls of squamous cells that the haemorrhages were found to occur (Fig. 9). It is clear that they came from the small capillary blood vessels in the centre of the whorls of underlying squamous epithelium. At this level the blood pigment was red and obvious. However, as the haemorrhages grew distally with the nail, they also passed superficially into the hard nail plate and here the blood pigment became much fainter (Fig. 10). As the haemorrhages passed distally and more superficially they gave a weaker reaction with the leuco-aniline blue technique. Methacrylate sections at right angles to the nail confirmed the blood capillaries in the centre of the whorls of squamous epithelium in the superficial part of the Malpighian layer to be the site of origin of haemorrhages in the nail (Fig. 11 and 12).

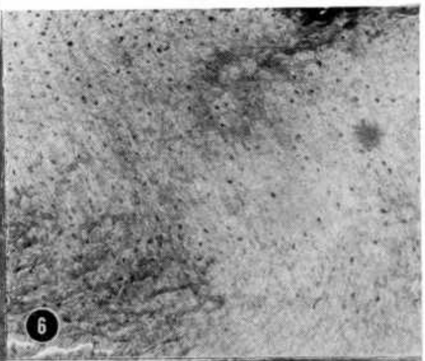
Discussion

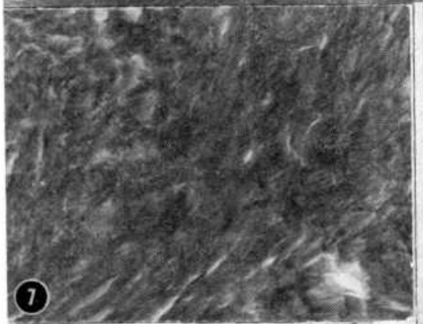
Two alternative hypotheses have been advanced to explain the appearance of the splinter haemorrhages described by Horder (1920). Some have ascribed them to increased capillary fragility (White, 1947; Lewis, 1948) while others believe them to be embolic in origin (Bramwell and King, 1942). By 1956 Wood had come to the conclusion that nail haemorrhages were not diagnostic of bacterial endocarditis. Our studies confirm that most nail haemorrhages are not embolic in nature for they do not remain stationary under the nail bed. They move with the nail thus showing that they are in its substance.

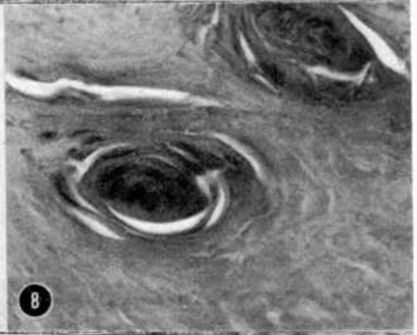
Platts and Greaves (1958) were the first to show that nail haemorrhages are to be found in the course of many diseases. They examined the fingernails of 429 patients and normal subjects and 35 cadavers. They found nail haemorrhages in a wide range of diseases other than subacute bacterial endocarditis, such as mitral stenosis, malignant tumours, and various pulmonary diseases. More significantly they found nail haemorrhages in several of their healthy acquaintances. They formed the impression that the haemorrhages were especially liable to occur after repeated jarring of the hand. Thus they found them in the nails of an emphysematous diabetic who was employed in making packing cases.

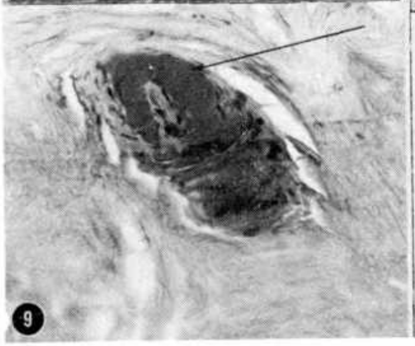
Gross and Tall (1963) found nail haemorrhages in no less than 19·1 per cent of 267 hospital inpatients. They were found to occur more often in those patients whose occupations exposed their hands to frequent trauma. They occurred more frequently in persons who had recently been admitted to hospital and fresh from the wear-and-tear of daily life and decreased with increasing length of duration in hospital when the patients had been at rest in bed. This suggested that the











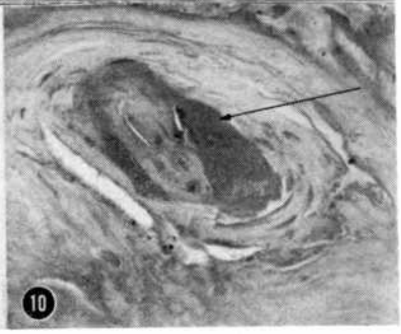


Fig. 5 *Nail haemorrhage in the right big toe of one of the authors (D.H.) on 1 January 1977. (×2·6.)*

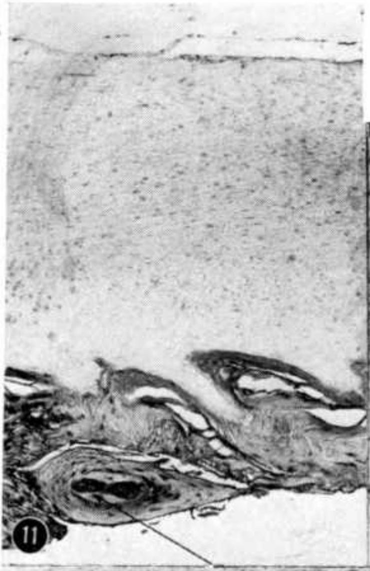
Fig. 6 *Superficial hard, nail plate. (Methacrylate section. Haematoxylin and eosin. ×100.)*

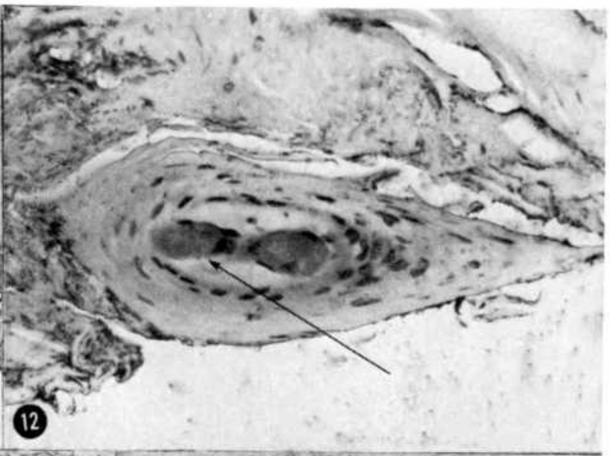
Fig. 7 *Deeper softer, nail plate. (Methacrylate section. Haematoxylin and eosin. ×250.)*

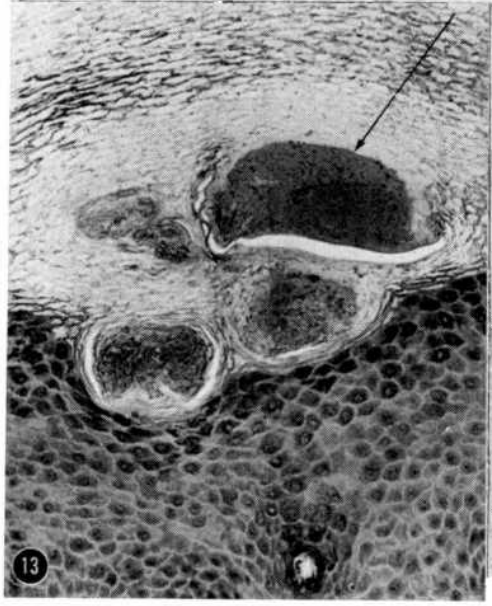
Fig. 8 *Whorls of squamous cells in the deep plate. (Methacrylate section. Haematoxylin and eosin. ×400.)*

Fig. 9 *Haemorrhage in the squamous whorls of the deep plate (arrow). (Methacrylate section. Haematoxylin and eosin. ×400.)*

Fig. 10 *An older, paler haemorrhage in the hard nail plate (arrow). (Methacrylate section. Haematoxylin and eosin. ×400.)*







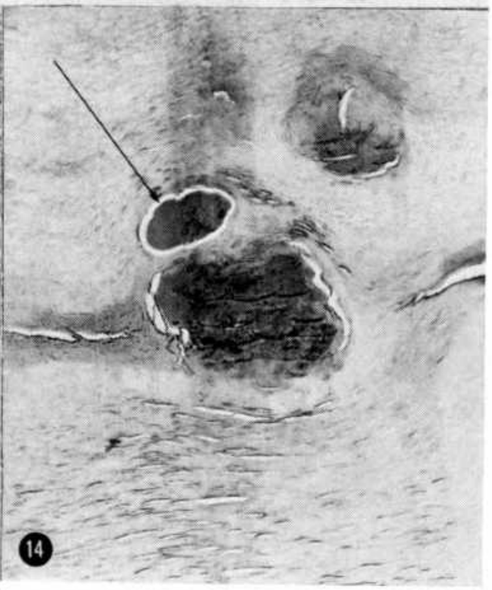


Fig. 11 *Methacrylate section taken at right angle to nail showing haemorrhage in squamous epithelium (arrow). (Haematoxylin and eosin × 92.)*

Fig. 12 *Haemorrhage in whorl of squamous cells underlying soft nail plate (arrow). (Haematoxylin and eosin × 240.)*

Fig. 13 *Section of skin of heel from a case of 'black heel'. Haemorrhages (arrow) have appeared in the deep keratin layer immediately overlying the Malpighian layer. (Haematoxylin and eosin × 150.)*

Fig. 14 *'Black heel'. The haemorrhages pass into the more superficial layers of keratin, gradually becoming paler. (Haematoxylin and eosin × 100.)*

haemorrhages were traumatic in origin. Other details recorded such as age, sex, temperature, systemic blood pressure, capillary fragility, and haematuria appeared to be irrelevant. Rennie (1974) noted the appearance of 50 linear haemorrhages under his fingernails and thumb nails during a restful evening at 5880 m but it should be noted that in the previous 5 weeks he had been engaged in high altitude climbing.

We also believe that the nail haemorrhages are traumatic in origin, for most occurred at the line of separation of the nail from the bed. Perhaps they are associated with leverage of the nail plate as it is pushed away from the underlying nail bed. They were commoner in the first three fingers on both hands which are used and exposed to trauma far more than the fourth and fifth fingers in which haemorrhages proved to be unusual. In this investigation on a right-handed person they were commoner in the right hand. Furthermore, only one haemorrhage occurred in the toenails over a period of 6 months consistent with the fact that the toes are relatively static and protected from trauma by the shoes. It is of interest that the solitary haemorrhage in the right big toe occurred after four long car journeys necessitating frequent pressure of the right foot on the accelerator pedal.

The view that the brown linear streaks in the nails are caused by minor haemorrhages finding their way into the nail plate is supported by a similar process leading to 'black heel' (Wilkinson, 1972) (Fig. 13 and 14). In this lesion closely aggregated groups of bluish-black specks occur suddenly at the back or side of the heel, just above the hyperkeratotic edge. They occur largely in athletic adolescents, in whom they may resemble a tattoo or even a melanoma, and are believed to arise as a result of small haemorrhages occurring after minor trauma which rupture superficial capillaries in the dermis. Blood pigment is subsequently eliminated through the epidermis and horny layer (Fig. 13 and 14), giving the appearance of the small black-brown marks.

It is our impression that the nail haemorrhages of highlanders are larger and originate lower down the nail (Fig. 1). It would be of interest to see if these differences from lowlanders are reproduced in patients exposed to hypoxaemia.

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Incidence of thyroid disease in cases of hypertrophic cardiomyopathy

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SUMMARY The investigative findings of patients considered to have possible hypertrophic cardiomyopathy were examined, and 31 of these fulfilling defined criteria for the disease were reviewed in detail, with emphasis on thyroid abnormalities. Four patients had a history of thyroid disease (13%). Explanations considered for the apparent association were the effects of hyperthyroidism on normal, or more probably, incipiently abnormal myocardium.

That hyperthyroidism may produce or precipitate hypertrophic cardiomyopathy (HOCM) has been suggested by Symons *et al.* (1974), who cited supporting clinical and necropsy evidence. A patient with both conditions excited our interest in 1971, since when thyroid function tests have been performed on patients with suspected or proven HOCM. We present here the findings in a series of 31 cases where the diagnosis was validated, with details of thyroid function tests, and the incidence of clinical thyroid disease.

Patients and methods

Angiocardiograms, echocardiograms, and haemodynamic data were initially examined, and patients with positive features were called for outpatient review between November 1976 and May 1977. A symptomatic history was taken, concentrating on symptoms suggesting past hyperthyroidism, and a family history, including thyroid and autoimmune disorders. Clinical examination, chest *x*-ray film, electrocardiogram, and echocardiogram were repeated, and blood taken for thyroxine (T3 and T4), TSH, T3 resin uptake, and thyroid antibody screening.

Because most patients, when examined, were taking beta-adrenergic blocking drugs, clinical signs were rejected as criteria for inclusion in the study. An adequate, diagnostic, left ventricular angiogram was accepted, where available, but other previously described features presented difficulty. Braunwald and Aygen (1963) pointed out that left ventricular (LV) outflow obstruction might be absent, while echocardiographic asymmetric septal hypertrophy is not pathognomonic, occurring in primary pulmonary hypertension (Goodman *et al.*, 1974), but absent in some otherwise typical cases. Similar doubts were cast, by Bulkley and Fortuin (1969) on systolic anterior movement of the anterior mitral valve leaflet while, in the absence of pulmonary hypertension, diastolic impingement of anterior mitral valve leaflet on the interventricular septum appears useful.

The agreed criteria were:
(1) Positive LV angiogram as defined by all of the following, (*a*) cone deformity ('carrot') of LV outflow tract; (*b*) septal bulge in left anterior oblique view (LAO); (*c*) normal or high ejection fraction, or
(2) Where angiographic views were inadequate or inappropriate (e.g. RAO projection) two of the following: (*a*) variable or latent LV outflow gradient exceeding 30 mmHg; (*b*) echocardiographic asymmetric septal hypertrophy with ratio 1·3 or more (Henry *et al.*, 1973a); (*c*) echocardiographic systolic anterior movement and diastolic septal impingement of anterior mitral valve leaflet.

Results

(1) PATIENT CHARACTERISTICS

Among the patients reviewed, 31 (16 female and 15 male) fulfilled the diagnostic criteria. The mean age was 40 years, with a range of 14 to 68 years. Twenty-five patients were symptomatic, complaining of dyspnoea (22 patients), chest pains (18 patients, 9 related to effort), palpitation (17 patients), and dizziness (14 patients); only 1 reported effort syncope.

As expected, clinical signs, under beta-blockade,

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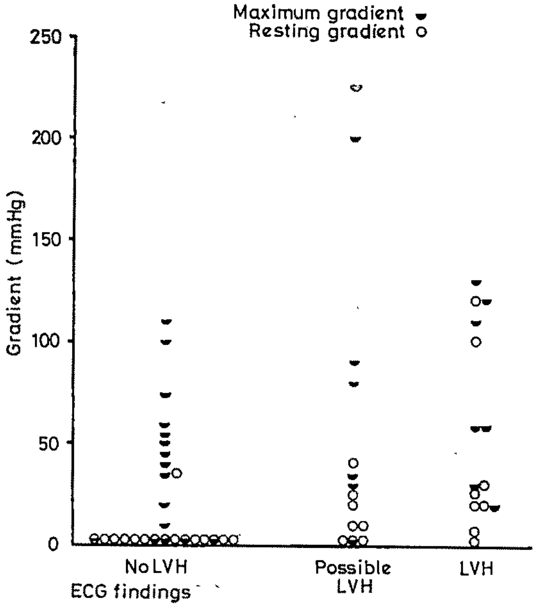

Fig. *Electrocardiographic LV hypertrophy as defined by computer programme (Bonner* et al., *1972) related to LV outflow gradients.*

were frequently non-diagnostic, though 21 patients showed a mid to late systolic murmur. Radiologically, 15 cases showed pulmonary venous congestion, but aortic dilatation was seen in one case only. Electrocardiograms showed 'anterior infarction' patterns in 7 cases, and 'inferior infarction' in 2. LV hypertrophy changes are related to LV outflow gradients in the Figure, and, as found by Walston *et al.* (1971), all cases but one with resting gradients showed some evidence of left ventricular hypertrophy. The Table shows haemodynamic data available on 29 patients, cases 1 to 4 being those with a thyroid disease history (see below).

(2) EVIDENCE FOR THYROID DISEASE

Apart from one of the patients with known thyroid disease, thyroid function tests at review were normal, and thyroid antibodies negative.

Four patients had a history of thyroid disorder, and, apart from these, no symptomatic history to suggest previous undiagnosed hyperthyroidism was obtained. Two patients recalled their fathers having a goitre, and there were 2 cases of goitre and 1 of myxoedema described in extended families.

Table *Haemodynamic data; gradients provoked using 5-10 μg isoprenaline (ISO)*

Case no.	*Sex*	*Pressure (mmHg)*				*Gradients (mmHg)*			
						Left outflow		*Right outflow*	
		Aortic	$\overline{PCV}$	*LVED*	$\overline{PA}$	*Resting*	*Isoprenaline*	*Resting*	*Isoprenaline*
1	F	170/80	8	10	20	0	0	0	20
2	M	160/70	5	8	20	0	0	0	25
3	F	130/80	13	—	—	0	45	0	0
4	F	120/80	6	5	19	0	75	—	—
5	M	95/60	2	3	7	5	60	50	95
6	M	120/75	15	16	25	30	60	—	—
7	F	115/70	9	12	14	0	10	—	—
8	M	120/75	—	15	24	Beta-blockade			
9	M	150/80	8	10	14	0	0	0	10
10	F	140/60	7	12	20	20	90	0	0
11	M	125/85	4	9	13	10	30	10	10
12	F	125/75	18	17	20	0	100	0	10
13	F	130/80	9	—	23	Beta-blockade			
14	M	130/90	12	10	—	35	55	15	30
15	F	200/100	25	40	—	0	0	10	10
16	M	100/50	17	26	18	40	225	9	15
17	F	70/35	22	17	34	90	230	—	—
18	F	125/85	8	12	20	0	20	0	0
19	M	140/77	6	2	13	10	80	15	30
20	M	140/80	7	5	12	0	40	—	—
21	F	155/88	13	—	24	0	10	0	0
22	M	75/50	5	7	14	20	30	0	15
23	F	115/70	11	12	14	0	60	4	10
24	M	125/75	15	14	20	20	110	10	25
25	F	140/80	15	18	20	0	110	0	12
26	M	100/70	9	12	11	0	200	0	0
27	M	180/110	13	—	—	120	120	—	—
28	F	160/90	22	45	40	25	25	—	—
29	F	170/90	7	8	15	0	45	0	0

Key to pressures: $\overline{PCV}$ mean pulmonary capillary venous (wedge), LVED left ventricular end diastolic, $\overline{PA}$ mean pulmonary artery.

(3) CASE HISTORIES

Case 1

A 49-year-old multiparous housewife was admitted in 1973, during an episode of chest pain, associated with sinus tachycardia and a blood pressure of 200/100 mmHg. Clinical LV hypertrophy was associated with a loud praecordial ejection systolic murmur. Electrocardiogram showed left bundle-branch block, and cardiac enzymes were normal. Serum T4 was 157 nmol/l with T3 resin uptake 94 per cent (then in the laboratory's hyperthyroid range) and 2-hour radioiodine uptake was confirmatory at 44 per cent.

Subsequent LV angiogram showed cone deformity of the outflow tract, septal bulge, and, though no left-sided gradient was shown, a right ventricular (infundibular) gradient of 20 mmHg was induced by isoprenaline. An adequate echocardiogram was not obtainable. Ten months treatment with carbimazole was effective, without ensuing recurrence of hyperthyroidism.

Case 2

A 61-year-old male paint tinter presented in December 1976, with a 3-month history of chest pain on effort, sweating, and the loss of 1·3 kg in weight. He showed a bounding pulse, BP 200/60 mmHg, a distinct ejection systolic murmur, and had a normal electrocardiogram. Serum T4 was 224 nmol/l (35 to 140) with free thyroxine index 298 (35 to 140) and T3 resin uptake 75 per cent (85 to 125). Left ventricular angiography showed cone deformity, septal hypertrophy, and increased ejection, while no LV gradient, but a right ventricular, infundibular gradient of 25 mmHg was provoked by isoprenaline. Echocardiography indicated systolic anterior movement, and septal impingement of anterior mitral valve leaflet, and asymmetric septal hypertrophy with a septum/free wall diastolic ratio of 2·0. All symptoms improved after treatment with radioiodine.

Case 3

A 35-year-old housewife complained in 1971 of episodic palpitation in her fourth pregnancy, and these persisted with effort chest pain after delivery, despite practolol therapy. Examination disclosed a normal pulse form, and an ejection systolic murmur. Electrocardiogram was normal, LV angiogram showing septal hypertrophy, with cone deformity, and a latent LV outflow gradient of 40 to 50 mmHg was shown with isoprenaline. There was echocardiographic asymmetric septal hypertrophy (ratio 1·37).

In 1973, her anxiety raised the question of hyperthyroidism, and serum T4 consistently exceeded 160 nmol/l (then in the laboratory's toxic range). Carbimazole resulted in improvement in anxiety, but not in angina. It was discontinued after 18 months, and, though free thyroxine index was slightly raised subsequently at 148, she was clinically euthyroid.

Case 4

This 68-year-old housewife was referred in 1976, after an outpatient visit for peripheral vascular disease, where a history of longstanding anginal symptoms and a systolic murmur were noted. She also reported exertional dizziness and weight loss. The pulse was bounding, BP 190/40 mmHg, and a grade 2 ejection systolic murmur was present. Electrocardiogram showed voltage criteria for LV hypertrophy, with lateral ischaemia. LV angiography showed a very small cavity, septal bulge, and outflow tract cone deformity, while a latent LV outflow gradient of 75 mmHg was seen with isoprenaline.

Serum T4 was 191 nmol/l (35 to 150) with T3 resin uptake 83 per cent and free thyroxine index 230 (35 to 150). Thyrotoxic symptoms recurred after 9 months carbimazole, and radioiodine uptake at 2 hours was increased at 48 per cent. Radioiodine therapy is now being considered.

Among patients excluded from the series because diagnostic criteria for HOCM were not entirely fulfilled, was one woman with a history of thyroid disease, though records of radioiodine therapy in 1961 were untraceable. She showed an increased ejection fraction on RAO angiogram, a variable LV outflow gradient reaching 120 mmHg with isoprenaline, and probable septal hypertrophy on poorly defined echocardiograms. TSH was increased at review, at 11·0 mU/l (less than 6·0).

Discussion

The difficulties of diagnosing clinically hyperthyroidism with HOCM have been outlined by Symons *et al.* (1974). Cardiac catheterisation findings in our cases were unremarkable, except that 2 of the patients with thyroid disease (cases 1 and 2) showed right ventricular, infundibular gradients in the absence of any left-sided gradient, a feature of only 2 other cases in the series.

It is difficult to validate clinical associations by comparison with controls in a series of this size, and we did not attempt this. Nevertheless, an incidence of 13 per cent of cases having thyroid disease appears largely to be a chance finding. If genuine, the connection has a number of possible explanations. One is that increased circulating thyroid hormones may produce HOCM in a previously normal heart. It has recently been shown, by Olsen *et al.* (1977), working with pregnant rats, that thyroxine analogues can produce, in the offspring, ultrastructural changes in the myocardium similar to those of HOCM. This was more pronounced with larger doses, and no such changes occurred in adult rats, even on high dose regimens. The connection with human disease is not clear, and a history of maternal thyroid disease was not noted in any of our patients. Electrocardiographic evidence of severe LV hypertrophy appears uncommon in thyrotoxic heart disease, though some myocardial hypertrophy (occasionally severe) is well recognised at necropsy. These observations accord with the cardiac effects of hyperthyroidism, probably arising from thyroid hormone activity, rather than induced catecholamine hypersensitivity (Aoki *et al.*, 1972).

Another possibility is that hyperthyroidism exacerbates or precipitates HOCM where there is an incipient myocardial abnormality. Symons *et al.* (1974) described 3 cases with both conditions, and in 2 of them myocardial histology indicated HOCM in 1, but was non-specific in the other.

Since even severe hyperthyroidism does not consistently result in HOCM, the second explanation appears the more probable, and the high incidence of echocardiographic abnormalities found by Henry *et al.* (1973b) in first degree relatives of HOCM patients suggests, firstly, that most, possibly all, cases have a hereditary basis, and, secondly, that some additional factor may be needed to produce clinical disease. Further information may accrue from echocardiographic screening of a thyrotoxic population.

We should like to thank Mrs C. Wrigley for performing the many additional echocardiograms.

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Severe pulmonary hypertension in advanced aortic valve disease

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SUMMARY Review of haemodynamic data of 151 cases with isolated aortic valve disease revealed severe pulmonary hypertension (pulmonary arterial systolic pressure of 60 mmHg or more) in 17 (11%). The left ventricular end-diastolic pressure was high in all but one case, suggesting that the severe pulmonary hypertension was a reflection of the late stages of aortic valve disease. The majority (64·7%) had a low cardiac index. Premature closure of the mitral valve was seen in 12 of the 17 patients. While the incidence of premature mitral closure was the same as in others with mild and moderate pulmonary hypertension, the average reversed ventriculoatrial gradient was higher in the latter groups.

Severe pulmonary arterial hypertension is considered uncommon in patients with aortic stenosis (Gorlin *et al.*, 1955; Gould *et al.*, 1973). In chronic aortic regurgitation, Goldschlager *et al.* (1973) found right heart failure in only 3 out of 126 cases.

The real incidence of pulmonary hypertension in isolated aortic valve disease has not been well documented and there are only a few reports dealing with selected groups of patients (Braunwald *et al.*, 1963; Lee *et al.*, 1970, 1971). This study in patients with isolated aortic valve disease was undertaken to establish the incidence of severe pulmonary hypertension and to examine the clinical and haemodynamic features of patients in whom it is present.

Subjects and methods

Out of 151 consecutive cases of isolated aortic valve disease who underwent cardiac catheterisation in our laboratory, 43 had a pulmonary arterial systolic pressure of 30 mmHg or more and a mean pressure more than 20 mmHg. The pulmonary arterial systolic pressure was 60 mmHg or more in 17 of these 43 cases; these constitute the group with severe pulmonary hypertension. The male:female ratio was 16:1. Ages ranged from 18 to 55 years with an average of 36·3 years. In addition to routine studies, each case had right and left heart catheterisation and selective angiocardiography. Left heart catheterisation was done through a brachial arteriotomy in all but 2 cases. In 1 case the left ventricle was entered by the transseptal route and in another percutaneous left ventricular puncture was necessary. Pressures were recorded with Statham P23 Db transducers and recorded on an Electronics for Medicine DR8 photographic recorder. The cases were divided into 3 groups according to the type of the valve lesion: 9 patients had pure aortic regurgitation, 5 had dominant aortic stenosis, and 3 had dominant aortic stenosis with significant aortic regurgitation. As one case record was misplaced, the clinical features were analysed in 16 of the 17 patients.

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Results

PRESENTING SYMPTOMS

The symptom common to all was exertional dyspnoea, with effort tolerance from grade 2 to grade 4. Eleven patients had paroxysmal nocturnal dyspnoea; 7 had exertional angina and 1 a history of syncope. Twelve of the 16 patients either gave a past history of congestive cardiac failure or presented in heart failure.

PHYSICAL SIGNS

The majority (11 patients) had considerable cardiac enlargement and all had a palpable left ventricular apical impulse. None had a separate left parasternal heave. The first heart sound was quiet in 6 patients with aortic regurgitation. The second heart sound was single in 3 and paradoxically split in 1; the pulmonary component was accentuated in 5 cases. A third heart sound was heard in 10 cases and a fourth heart sound in 2. An apical mid-diastolic murmur was heard in 9 patients, but only in those with aortic regurgitation.

ELECTROCARDIOGRAM

The electrocardiograms of 15 patients were analysed. All were in sinus rhythm. Six patients (40%) had a normal frontal QRS axis (0 to +90°), and in 5 of these the axis was between 0 and +30°. In 6 cases (40%) the axis was 0 to −30° and in 3 (20%) between −30 and −90°. No patient had right axis deviation. A prolonged PR interval was found in 4 (26·6%). Left atrial enlargement was present in 10 patients (66·6%) while right atrial enlargement was present in only 1. None had electrocardiographic evidence of right ventricular hypertrophy. All had left ventricular hypertrophy while 3 had complete left bundle-branch block. An infarct pattern was seen in 2 cases (13%) of aortic regurgitation.

CHEST X-RAY FILM

In only 2 patients was there enlargement of the main pulmonary artery and its pulmonary branches. In 40 per cent, there was slight to moderate left atrial enlargement. Pulmonary venous congestion was seen in all.

HAEMODYNAMIC DATA

The Table summarises the haemodynamic data in all 17 patients. The majority (64·7%) had a low cardiac index (below 2·4 l/min per m^2) and a wide arteriovenous oxygen difference. The mean pulmonary arterial pressure was more than 40 mmHg in all. The pulmonary arteriolar resistance was 5 units × m^2 or more in all but 1 patient. Though the cardiac index and pulmonary arterial systolic pressure did not show a linear relation, the patients with higher pulmonary arterial pressures had a lower cardiac index. Of 17 cases, 8 had a raised right ventricular end-diastolic pressure (more than 8 mmHg). All but 1 had a very high left ventricular end-diastolic pressure and pulmonary artery wedge pressure, but there was no linear relation between left ventricular end-diastolic pressure and pulmonary arterial systolic pressure. Simultaneous left ventricular and pulmonary artery wedge pressure recordings in 10 patients showed a reversal of the atrioventricular gradient in 8 and this was seen in another 4 in immediately consecutive recordings. Thus, in 12 out of 17 cases there was haemodynamic evidence of premature closure of the mitral valve. Premature closure of the mitral valve occurred in all the three groups, pure aortic regurgitation, dominant aortic stenosis, and mixed aortic valve disease. Patients with premature closure of the mitral valve had a slightly lower cardiac index (average 2·12 l/min per m^2) compared with those without it (average 2·47 l/min per m^2).

CINEANGIOGRAPHY

Left ventriculography revealed poor contractility in all, with a reduced ejection fraction in those in whom it could be calculated. Two patients showed diastolic mitral regurgitation.

Table *Cardiac catheterisation data*

No.	*Diagnosis*	*PA* (*mmHg*)	*LVEDP* (*mmHg*)	*PW* (*mean*) (*mmHg*)	*CI* (*l/min per m^2*)	*AV O_2* (*vol%*)	*PMC*	*PAR* (*units × m^2*)
1	AR	60/30 (40)	20-40	36	1·04	7·3	No*	2
2	AR	60/35 (45)	20-25	22	3·8	4·8	No*	11·9
3	AR	76/36 (50)	50	36	2·9	4·0	Yes*	5
4	AR	80/40 (50)	12	5	1·7	9·7	Yes*	15
5	AR	70/45 (52)	45	36	2·0	8·6	Yes*	8
6	AR	70/36 (45)	30	28	2·0	8·2	Yes*	8·5
7	AR	105/55 (72)	35-40	40	1·5	8·2	Yes*	21·3
8	AR	60/35 (43)	55	25	2·4	7·0	Yes	6·8
9	AR	72/12 (50)	36	30	1·9	6·2	Yes	10
10	AS ar	100/38 (58)	30	22	2·0	6·5	Yes	19
11	AS ar	80/35 (50)	36	36	3·6	4·7	No	8
12	AS ar	60/30 (40)	30	23	2·7	5·8	Yes*	6·3
13	AS ar	77 (RV)†	30-50	—	1·3	8·7	—	—
14	AS	60/30 (40)	15-20	28 (LA)	1·45	11·8	Nodal rhythm	8·3
15	AS AR	100/36 (59)	35	29	2·01	6·4	Yes	15
16	AS AR	86/44 (56)	36	19	1·8	6·7	Yes	29
17	AS AR	70/30 (45)	36	28	2·6	5·5	Yes	6·5

PA, pulmonary artery pressure (mmHg); LVEDP, left ventricular end-diastolic pressure (mmHg); PW, pulmonary artery wedge pressure (mean) (mmHg); CI, cardiac index (l/min per m^2); AV O_2, arteriovenous O_2 difference (vol%); PMC, premature mitral valve closure; PAR, pulmonary arteriolar resistance (units × m^2); AR, aortic regurgitation; AS, aortic stenosis; AS AR, aortic stenosis and aortic regurgitation; AS ar, dominant aortic stenosis with mild aortic regurgitation.

* Simultaneous left ventricular and pulmonary artery wedge pressure recording.

† PA not entered.

Discussion

Severe pulmonary hypertension is considered an uncommon haemodynamic finding in patients with isolated aortic valve disease (Gorlin *et al.*, 1955; Gould *et al.*, 1973). The presence of pulmonary hypertension however is likely to be related to the stage of the disease, and to reflect the left ventricular end-diastolic pressure. Braunwald *et al.* (1963) found a pulmonary arterial systolic pressure higher than 30 mmHg in 11 per cent of patients with aortic stenosis, but the number with a pressure over 60 mmHg was not indicated. In the present series, 43 out of 151 (28·4%) patients had a pulmonary arterial systolic pressure over 30 mmHg. Lee *et al.* (1970) reported that 14·7 per cent of 34 patients with aortic stenosis had a pulmonary arterial systolic pressure more than 60 mmHg. In another report they found that 2 of 10 patients with severe aortic regurgitation had a pulmonary arterial systolic pressure more than 60 mmHg (Lee *et al.*, 1971). The present study showed an 11 per cent incidence of severe pulmonary hypertension (more than 60 mmHg pulmonary arterial systolic pressure) in an unselected group of 151 patients with aortic valve disease.

The cardiac index was low in the majority (64·7%) of our patients, and in all but 1 the left ventricular end-diastolic pressure was high. This suggests that the pulmonary hypertension was a manifestation of a late stage of aortic valve disease. It is not surprising that there was no linear relation between the end-diastolic pressure and pulmonary arterial systolic pressure. It is known that once the left atrial mean pressure exceeds 25 mmHg, the increase in pulmonary arterial pressure does not maintain a linear relation with the increase in left atrial pressure. The pulmonary arterial pressure increases more than expected, because of the development of active pulmonary vasoconstriction (Dexter *et al.*, 1950). The pulmonary arteriolar resistance was raised in all but one of our patients.

In the present series, 12 out of 17 cases with severe pulmonary hypertension showed premature closure of the mitral valve with reversed diastolic gradient between 2·6 and 6 mmHg. It is well known that premature closure of the mitral and tricuspid valve occurs in severe aortic regurgitation (Spring *et al.*, 1972). Premature closure of the mitral valve has been thought to protect the pulmonary vascular bed from aortic regurgitant flow and consequent raised pressures (Rees *et al.*, 1964; Spring *et al.*, 1972). To verify this hypothesis, we compared these patients with severe pulmonary hypertension with those with mild and moderate pulmonary hypertension in association with isolated aortic valve disease. Of 151 patients, 19 had mild pulmonary hypertension (pulmonary arterial systolic pressure more than 30 mmHg, but less than 40 mmHg, and mean pulmonary artery pressure more than 20 mmHg) and 7 had moderate pulmonary hypertension (pulmonary artery systolic pressure more than 40 mmHg, but less than 60 mmHg). In the mild pulmonary hypertension group, 12 out of 19 patients had premature mitral closure with reversed ventriculoatrial gradient between 2 and 22 mmHg (average 8·7 mmHg). The patients with moderate pulmonary hypertension showed premature mitral closure in 6 of 7 cases, with reversed gradient between 5·5 and 13 mmHg (average 8·9 mmHg). Thus in the patients with mild and moderate pulmonary hypertension taken together the incidence of premature closure of the mitral valve (70%) was the same as in the group with severe pulmonary hypertension (70%). However, the average reversed gradient was higher in the former group (8·8 mmHg) than in the latter group (4·6 mmHg). The present study shows that premature closure of the mitral valve does not always prevent the development of pulmonary hypertension. However, patients with larger reversed ventriculoatrial gradients had a lower degree of pulmonary hypertension. In this series premature mitral closure occurred in patients with aortic regurgitation, in those with aortic stenosis, and with combined lesions. Mild to moderate diastolic mitral regurgitation has been reported to occur frequently (96% of cases) in aortic regurgitation with premature closure of the mitral valve (Spring *et al.*, 1972). In some patients with aortic regurgitation, the Austin-Flint murmur has been attributed to diastolic mitral regurgitation (Lochaya *et al.*, 1967).

The quiet first heart sound in aortic regurgitation can also be explained by premature closure of the mitral valve (Meadows *et al.*, 1963). The fourth heart sound in aortic regurgitation with a quiet or absent first heart sound may be the premature closure sound of the mitral valve (Wigle and Labrosse, 1965). Spring *et al.* (1972) attribute it to forcible atrial contraction against a closed mitral valve.

A prolonged PR interval has been reported to be a frequent finding in cases with aortic regurgitation (Herbert, 1967). In the present series, 4 cases had a prolonged PR interval. A prolonged PR interval in such a situation ensures early left atrial contraction (relative to ventricular systole), so that its contribution to the forward flow is not affected by premature closure of the mitral valve (Herbert, 1967).

In patients with isolated aortic valve disease, the clinical examination more often provides a clue to the presence of pulmonary hypertension, than does radiological examination or the electrocardiogram. While a palpable right ventricular heave was not found, in 5 cases the pulmonary component of the second sound was accentuated. The electrocardiogram analysis showed neither right axis deviation nor right ventricular hypertrophy (by voltage criteria) in any patient. Wood (1958) analysed 250 cases of aortic stenosis and observed that the electrocardiogram was normal in trivial and most moderate cases. In severe cases, left ventricular preponderance with secondary T wave inversion was found in 80 per cent, and left bundle-branch block in 14 per cent of patients. Mitchell *et al.* (1954) reviewed 88 cases of pure aortic stenosis and found that in 84 per cent there was electrocardiographic evidence of left ventricular hypertrophy, but in none was there right ventricular hypertrophy. Gould *et al.* (1973) in their single case of aortic stenosis with right heart failure observed right axis deviation.

The pathogenesis of pulmonary hypertension in aortic valve disease appears to be similar to that in mitral valve disease. The raised left atrial pressure, secondary to the raised left ventricular end-diastolic pressure, in the first place leads to a passive increase in pulmonary arterial pressure and later to reactive vasoconstriction. McHenry *et al.* (1974) reported 7 patients with severe aortic stenosis and increased pulmonary arteriolar resistance (more than 7·9 units × m^2), who deteriorated suddenly after catheterisation. Postoperative study in 2 survivors showed that pulmonary vascular resistance had returned to normal, thus confirming that earlier pulmonary hypertension had been the result of reactive vasoconstriction.

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Familial sinus node dysfunction with autosomal dominant inheritance

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SUMMARY A large family with sinus node dysfunction is described, spanning three generations and with an autosomal dominant trait. There was an obvious association between the grade of mental retardation and the severity of the sinoatrial disorder.

Recently, the high prevalence of systemic embolism in chronic sinoatrial disorders or so-called 'sick sinus syndrome' has been stressed (Fairfax *et al.*, 1976). In their series of 100 patients with this syndrome, only 2 cases were familial. A few familial cases were also reported in other series of patients with the sick sinus syndrome (Rokseth *et al.*, 1970; Rokseth and Hatle, 1974) and it appears that approximately 2 to 6 per cent of cases are inherited. There are already 4 extensive reports on family pedigrees showing this syndrome to be an autosomal trait in one to three generations (Spellberg, 1971; Livesley *et al.*, 1972; Caralis and Varghese, 1976; Jagovella *et al.*, 1976). We report on a very large family with chronic sinoatrial disorders occurring in three generations. Some of the members of the family died suddenly and had had mental retardation as well as sinus node dysfunction. In one woman with the tachycardia-bradycardia syndrome, tachycardia was induced by emotional stimuli and it was necessary to implant a permanent pacemaker.

Case report and family history (Fig.)

A 37-year-old woman was admitted to our intensive care unit immediately after delivery of her seventh child, with a life-endangering tachycardia-bradycardia syndrome and recurrent atrial fibrillation. The patient was of poor intelligence and had no understanding of her disease. The tachycardia could be repeatedly triggered by slight psychological stress and treated by reassurance. We finally installed an endocardial pacemaker system and also treated her with digitalis and sedatives. Four days later a severe pulmonary embolism occurred, from which she recovered slowly. Her condition then improved greatly and she was able to look after her home and 7 children.

Her mother, who gave birth to 11 children, had had a cardiac arrhythmia from childhood and died of sudden cardiac arrest. Early electrocardiograms showed sinus bradycardia (35/min), and later records also showed atrial fibrillation.

Three brothers had persistent atrioventricular dissociation. One of the brothers with atrioventricular dissociation also had second degree atrioventricular block and died unexpectedly at the age of 38. Necropsy showed no cardiomegaly and no evidence of cardiomyopathy or severe coronary heart disease (heart weight 550 g). Another brother had repeated episodes of loss of consciousness, though his electrocardiogram showed only incomplete right bundle-branch block at rest. One sister had atrioventricular dissociation and intermittent 2:1 atrioventricular block. Two brothers and one sister died in infancy of unknown cause, one brother was not examined, and one sister was in good health.

Of the 7 children of our patient, 4 have intermittent sinoatrial or atrioventricular block, with attacks of dizziness.

An association was observed between the arrhythmia and mental retardation in the children, and 3 brothers were also mentally retarded.

Discussion

Inherited sinus node dysfuction is not specifically mentioned but its presence can be inferred in numerous reports of pedigrees of patients with multiform arrhythmias. Some members of these

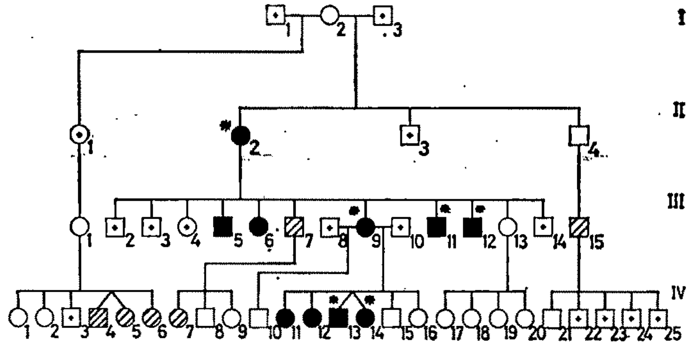

Fig. *Pedigree of family with inherited autosomal dominant sick sinus syndrome.*
○ □ *normal electrocardiogram,* ● ■ *electrocardiogram showing features of sick sinus syndrome* (*) *or AV heart block,* ⊘ ▨ *minor electrocardiographic abnormalities without specific features of sick sinus syndrome,* ⊙ ⊡ *no electrocardiogram.*

I. 3 = muscular dystrophy of shoulder girdle type.
II. 2 = sinus bradycardia (35/min), later atrial fibrillation.
III. 5, 6 = atrioventricular dissociation, second degree atrioventricular block (III. 5 sudden death).
III. 7 = incomplete right bundle-branch block, syncopal attacks.
III. 9 = sinus bradycardia (35/min), with atrial fibrillation and paroxysmal ventricular tachycardia.
III. 11, 12 = atrioventricular dissociation.
III. 15 = sinus bradycardia (less than 50/min).
IV. 4, 5, 6, 7 = sinus bradycardia (less than 50/min).
IV. 11 = intermittent second degree atrioventricular block (3 : 1).
IV. 12 = intermittent second degree atrioventricular block (2 : 1).
IV. 13 = episodes of sinus arrest.
IV. 14 = episodes of sinus arrest, intermittent second degree atrioventricular block (2 : 1).

families showed persistent atrial standstill, sinus bradycardia, atrial fibrillation, atrioventricular nodal rhythm with atrioventricular dissociation, or complete heart block (Bacos *et al.*, 1960; Phair, 1963; Khorsandian *et al.*, 1964; Gazes *et al.*, 1965; Allensworth *et al.*, 1969; Gault *et al.*, 1972). Electrocardiograms of first degree relatives of unselected patients with complete atrioventricular block have been examined and conduction abnormalities found in 10 per cent (Morgans *et al.*, 1974). Family screening thus appears to be desirable in cases of aetiologically unexplained disorders of heart rhythm and also after unexpected death in young adults.

In the family described here, the sinoatrial disorders were already evident in childhood. The evolution from sinus bradycardia to atrial fibrillation and sudden death was documented in the mother.

The exact cause of familial sick sinus syndrome is unknown. In some cases, morphological changes in the sinus node artery (James, 1967), sinus node fibrosis, or necrosis of atrial cells (Allensworth *et al.*, 1969) have been observed. In a large series of patients with the sick sinus syndrome, however, there were no striking alterations of the sinus node artery, at least angiographically (Engel *et al.*, 1975). An enzyme deficiency has been postulated, but such 'inborn errors of metabolism' are usually recessive traits, whereas familial heart arrhythmias are autosomally dominant. Familial muscle dystrophies have also been associated with the sick sinus syndrome, and our patient's maternal grandfather suffered from muscular dystrophy with onset in the shoulder girdle. None of his offspring, however, showed any evidence of muscle disease.

Caralis and Varghese (1976) recently put forward the suggestion that an increase in vagal tone may be responsible for familial sinus node dysfunction. Thus, these patients may be hypersensitive to normal phasic vagal stimulation (Dighton, 1975). This hypothesis is supported by one case of sick sinus syndrome in a family with prolonged PR interval (Gambetta *et al.*, 1973). On the other hand, patients with the familial QT prolongation syndromes with and without deafness (Jervell-Lange-Nielsen syndrome, Romano-Ward syndrome) may have a reduced sympathetic tone. An altered sympathetic nerve response unrelated to the heart has also been reported (Ziegler *et al.*, 1976). If this dysfunction of the autonomic nervous system affecting vagal and/or sympathetic tone is a possible explanation, then familial sick sinus syndrome may be the result of either nodal hypersensitivity to normal phasic stimulation (as in our patient) or overstimulation ('vagal epilepsy') caused by an unstable cerebral focus. Lown *et al.* (1976) gave an excellent description of a case showing ventricular fibrillation caused by emotionally determined sympathetic nervous discharge. Similarly, the life-threatening tachycardias in our patient were obviously influenced by psychological factors.

Because of the possibility that a familial dysfunction of sympathetic or vagal tone may be a cause of cardiac arrhythmias, the use of psychotropic drugs and psychotherapy should be considered in these cases. In addition, when discussing the genesis of rhythm disorders in an individual patient, one should consider personal, psychological, and genetic factors.

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Wolff-Parkinson-White syndrome (type A) complicated by heart block in both normal and accessory pathways

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SUMMARY A 67-year-old man with Wolff-Parkinson-White syndrome type A presented with second degree atrioventricular block in the anomalous pathway and complete infra-Hisian block in the His-Purkinje pathway. He had increasingly frequent attacks of dizziness not related to exercise. A permanent ventricular demand pacemaker was successfully implanted following intracardiac electrophysiological studies.

Disorders of conduction occurring simultaneously in both normal and abnormal atrioventricular pathways of patients with the Wolff-Parkinson-White syndrome have only rarely been observed (Lev *et al.*, 1966). Intracardiac studies to reveal the underlying electrophysiological mechanisms have been undertaken in a few such cases with iatrogenic or congenital (nodal) atrioventricular block in the nodal-His-Purkinje pathway (Coumel *et al.*, 1973; Seipel *et al.*, 1976).

We report a case of Wolff-Parkinson-White syndrome type A presenting with episodes of dizziness caused by combined conduction abnormalities in both the normal and the accessory atrioventricular pathways. An unusual feature was that the normal pathway was blocked below the His bundle.

Case report

A 67-year-old man was referred with transient episodes of dizziness over a period of 6 years. Attacks occurred at rest and were not induced by exercise. No episodes of complete syncope had occurred and there was no history of paroxysmal tachycardia in childhood or adult life.

An electrocardiogram showed Wolff-Parkinson-White syndrome type A with maximal ventricular pre-excitation, intermittent second degree atrioventricular block and a PR (P-delta) interval of 0·14 s for conducted sinus beats (Fig. 1). Second degree atrioventricular block usually followed slowing of the sinus rate. His bundle recordings (Scherlag *et al.*, 1969) showed intermittent 2:1 conduction of sinus beats across the accessory pathway when the atrial rate fell below 80 per minute. Conducted sinus beats were preceded by a His potential with an HV interval (His spike to earliest ventricular activity) of 25 ms. Sinus beats not conducted in the accessory pathway were completely blocked after the His potential (infra-Hisian block, Fig. 2A). Right atrial pacing at a cycle length of 485 ms (124 beats/min) induced a normal atrioventricular response, the AH interval increasing from 120 ms (upper limit of normal range) during spontaneous rhythm to 155 ms. The apparent HV interval of conducted beats shortened from 25 ms to 0 ms during incremental atrial pacing, without further widening of the QRS complex. Ventricular activation never occurred by the normal pathway. One-to-one anterograde accessory pathway conduction occurred at atrial pacing rates up to 150 beats per minute, during which the A-delta conduction interval increased from 145 to 155 ms (Fig. 2B). Ventricular pacing showed no retrograde conduction in either the normal or accessory pathway.

A permanent ventricular demand pacemaker was implanted, initially with an endocardial electrode but this was unstable and was later replaced by an epicardial one. The patient has had no more attacks of dizziness (follow-up 9 months).

Discussion

In patients with the Wolff-Parkinson-White syndrome and sinus rhythm the ventricle is activated

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[2] In receipt of a British Heart Foundation grant.

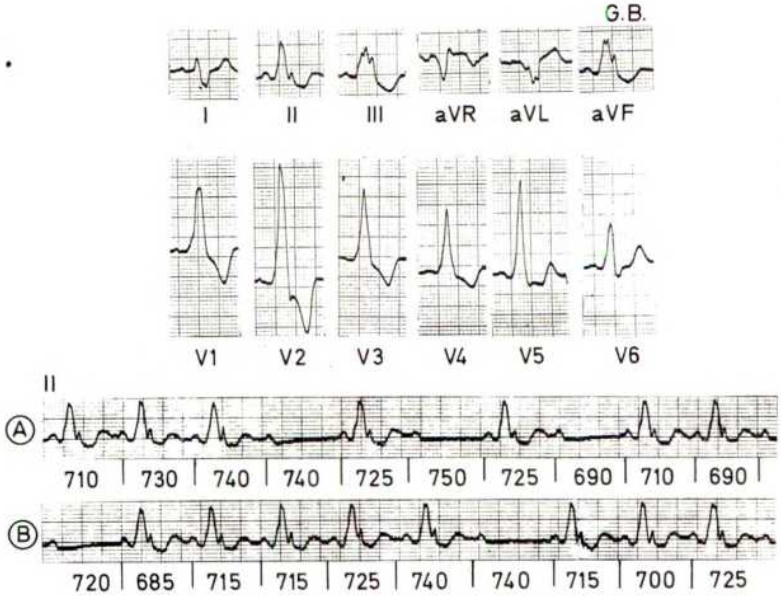

Fig. 1 *Electrocardiogram in spontaneous rhythm showing second degree block and pattern of pre-excitation.*

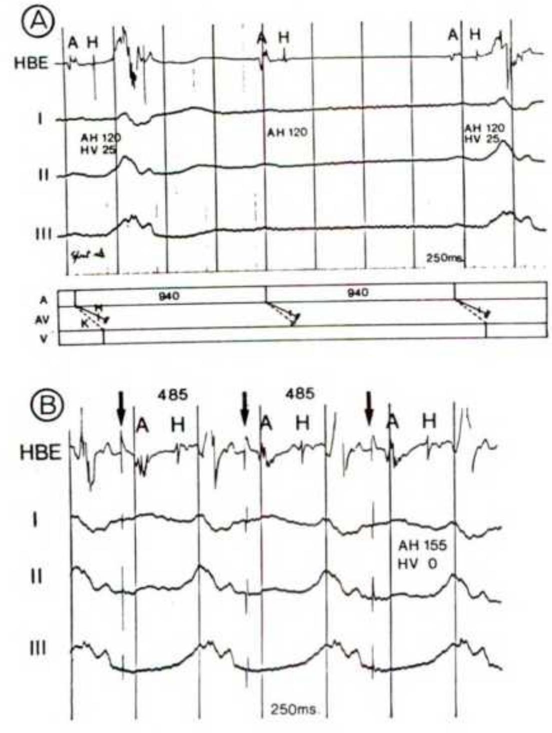

Fig. 2 *His bundle electrogram (HBE) and three surface leads. (A) spontaneous rhythm; (B) atrial pacing at 124 beats per minute. Conduction is now 1:1. HV interval is now zero but the QRS morphology is unchanged indicating that conduction must be down the aberrant pathway in sponataneous rhythm and with atrial pacing.*

typically via two atrioventricular pathways; one is the normal His-Purkinje pathway and the other is the abnormal accessory pathway. The QRS configuration of the fusion beats recorded on the surface electrocardiogram indicates the relative times required for sinus impulses to be conducted to the ventricle 'in parallel' down both the normal and accessory atrioventricular pathways. Usually both incremental atrial pacing and premature atrial beats prolong conduction selectively in the normal atrioventricular nodal pathway causing more ventricular excitation via the accessory pathway. This results in further widening of the QRS complex. In our case a pattern of total ventricular pre-excitation was apparent on the electrocardiogram. The stability of QRS configuration during incremental atrial pacing confirmed that the accessory pathway was exciting most or all of the ventricle. This in association with revealed infra-Hisian block in the normal pathway during nonconducted sinus beats indicated complete heart block rather than second degree block in the nodal-His-Purkinje pathway. Both the aetiology and the duration of the infra-Hisian block were unknown. The second degree block in the accessory pathway appeared to be bradycardia dependent, occurring usually at sinus rates of less than 80 beats per minute. Electrocardiograms were not obtained during attacks of dizziness and higher degrees of block in the accessory pathway were never seen.

Combined conduction disturbances in both the accessory and the normal atrioventricular pathways have only rarely been seen in patients with the Wolff-Parkinson-White syndrome (Seipel *et al.*, 1976). The block in each pathway may be only for anterograde conduction or only for retrograde conduction. Several previous reports have emphasised the superiority of retrograde accessory pathway conduction to anterograde accessory pathway conduction (Coumel *et al.*, 1973; Dreifus *et al.*, 1968; Massumi, 1970). Supranormal conduction down an accessory pathway in association with normal conduction occurring in the nodal-His pathway has also been described (Coumel *et al.*, 1973; McHenry *et al.*, 1966). In our case retrograde conduction of ventricular impulses failed to occur across either the normal or the accessory pathways, nor was supranormal conduction in either pathway seen following premature atrial beats.

Patients with the Wolff-Parkinson-White syndrome and combined conduction disturbances rarely complain of symptoms of bradycardia. One of four patients previously reported by Coumel *et al.* (1973) presented with an episode of altered consciousness, but this was attributed to sinus node disease rather than an atrioventricular conduction disturbance. In the case reported by Dreifus *et al.* (1968) symptomatic complete heart block requiring ventricular pacing occurred after ligation of the His bundle for recurrent re-entry tachycardias. Their explanation was that the accessory pathway had also been ligated.

A patient similar to ours with complete block in the normal pathway and second degree block in the accessory pathway has been described (Seipel *et al.*, 1976); the site of this block in the normal pathway was the atrioventricular node, but in contrast the block in our patient was below the His bundle. A common feature was the absence of episodes of loss of consciousness (Adams-Stokes attacks) in spite of frequent episodes of dizziness. This probably depended upon improvement in accessory pathway conduction following reflex increases in the sinus rate. Without the assurance that this protective mechanism would always occur, and because of increasingly frequent attacks of dizziness in our otherwise healthy patient, permanent demand ventricular pacing was undertaken. Electrocardiograms have subsequently shown continuous ventricular pacing without retrograde atrial activation.

The occurrence of rapid ventricular rates caused by 1:1 conduction across the accessory pathway during atrial tachycardia is a well recognised complication in some patients with the Wolff-Parkinson-White syndrome. This case illustrates a contrasting problem: that of conduction block occurring simultaneously in both the normal and the accessory atrioventricular pathways. The electrophysiological properties of an accessory pathway may vary considerably from moment to moment. When this untrustworthy pathway is the only route of conduction to the ventricle, continuous acceptable function cannot be assumed.

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Echocardiographic sign of right-sided hypertrophic obstructive cardiomyopathy

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SUMMARY The echocardiographic and haemodynamic findings in a patient with hypertrophic obstructive cardiomyopathy (HOCM) and dynamic subpulmonary stenosis, without left ventricular gradient, are described. The echocardiogram shows not only asymmetric septal hypertrophy, systolic anterior movement of the anterior mitral leaflet, and midsystolic collapse of the aortic valve, but also increase in the right ventricular wall echoes and systolic collapse of the pulmonary valve.

We believe that in the absence of pulmonary hypertension these signs, particularly the systolic closing movement of the pulmonary valve cusp, may suggest right ventricular obstruction in HOCM.

The M-mode echocardiographic features of hypertrophic cardiomyopathy with (Shah *et al.*, 1969; Henry *et al.*, 1973b) and without (Henry *et al.*, 1973a) left ventricular outflow tract obstruction are well established. The case reported here suggests that associated right ventricular obstruction (Lockhart *et al.*, 1966; Befeler *et al.*, 1973) can be identified by single dimension echocardiography.

Case report

A 15-year-old boy presented with effort dyspnoea. The peripheral pulses were slightly jerky, the blood pressure was 120/80 mmHg, and the jugular venous pressure was normal, with a dominant *a* wave. A sustained right ventricular impulse was palpable and there was a grade 3/4 ejection systolic murmur which became louder on inspiration and quieter with the Valsalva manoeuvre.

The electrocardiogram showed probable biatrial hypertrophy and severe right ventricular hypertrophy with 3 mm ST segment depression in right praecordial leads. The plain chest *x*-ray film showed mild pulmonary venous dilatation but normal heart size.

At right and left heart catheterisation, the pulmonary artery pressure was 20/11 (mean 15) mmHg; simultaneous recording in the right ventricular inflow and outflow tracts showed a 20 mmHg systolic gradient. No gradient was recorded in the left ventricular cavity at rest, during catecholamine administration, or after ectopic beats. Right and left ventriculography (Fig. 1a, b) showed protrusion of the interventricular septum into both ventricular outflow tracts; this was more conspicuous on the right side. Left ventricular outflow tract obstruction was not seen, but infundibular obstruction resulting from hypertrophy of the crista supraventricularis and thickening of the septum was clearly defined. The pulmonary valve cusps were normal.

Right heart echocardiography (Fig. 2) demonstrated systolic flutter with striking mid-systolic collapse of the pulmonary valve, abnormally strong septal echoes behind the pulmonary valve, and thickening of the right ventricular anterior wall. Echocardiograms from the left heart (Fig. 3a and b) showed a thick interventricular septum (septal/left ventricular posterior wall ratio > 1·5/1), a small left ventricular cavity, diastolic contact between the mitral anterior leaflet and the septum, anterior systolic motion of the mitral apparatus, and systolic collapse of the aortic cusps.

Discussion

Hypertrophic cardiomyopathy is classically associated with predominant left-sided obstruction, but isolated (Morrow *et al.*, 1969) and dominant (Befeler *et al.*, 1973) right ventricular outflow tract obstruction have been described. Though in the present case no left ventricular gradient was recorded, the left heart echocardiographic findings, particularly systolic collapse of the aortic cusps (Fig. 3b), suggest that left ventricular obstruction

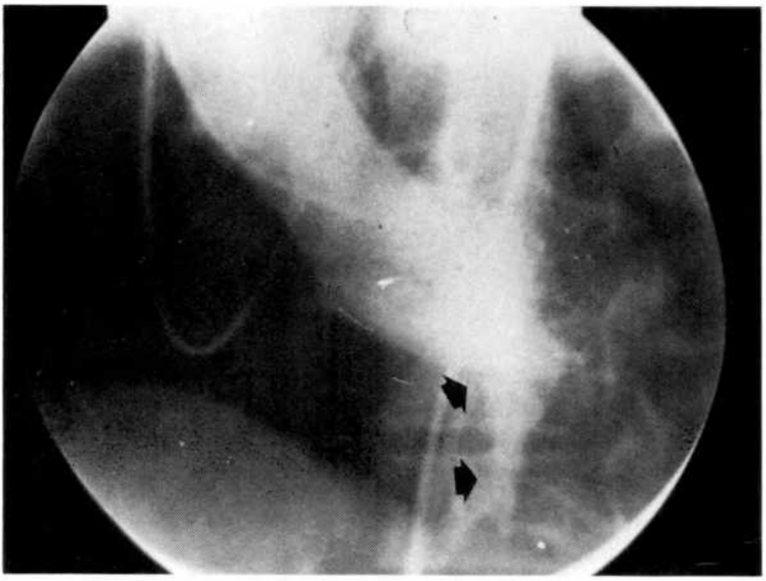

Fig. 1a

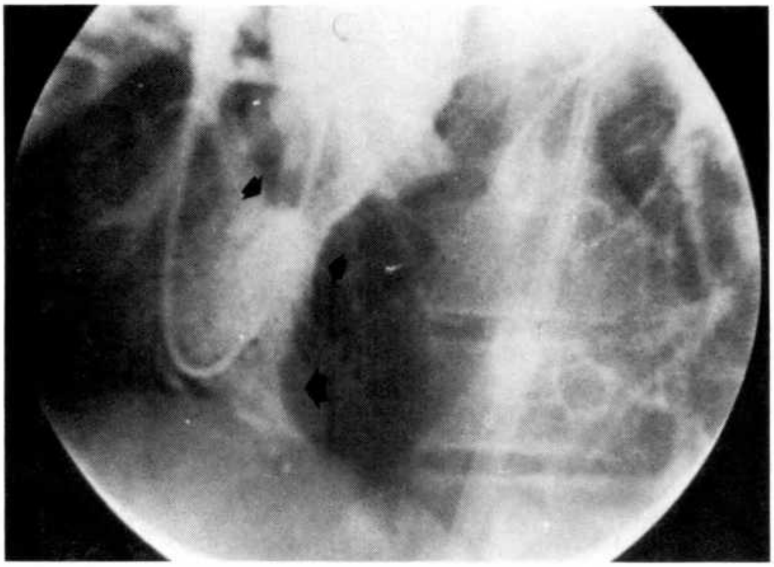

Fig. 1b

Fig. 1 (*a*) *Left ventriculogram in systole (left anterior oblique). The asymmetric septal hypertrophy is seen (arrows), with wide outflow tract.* (*b*) *Right ventriculogram in systole (left anterior oblique). The predominantly right-sided septal protrusion is observed (lower arrows), as well as cristal hypertrophy causing infundibular stenosis (top arrow).*

was present at the time of the ultrasonic examination. It thus seems reasonable to conclude that this patient had hypertrophic cardiomyopathy with dominant left ventricular outflow tract obstruction.

Systolic collapse of the pulmonary valve has been shown echocardiographically in pulmonary hypertension (Weyman *et al.*, 1974) and isolated infundibular stenosis (Nanda *et al.*, 1975) but has not previously been reported in hypertrophic cardiomyopathy. In this case it occurred with, and presumably reflected, conspicuous infundibular obstruction. Whether this echocardiographic finding can reliably identify the right-sided obstruction commonly associated with predominantly left-sided obstructive cardiomyopathy (Swan *et al.*, 1971) is a matter for further investigation. The observations reported here do, however, suggest that examination of the pulmonary valve might usefully be included in the echocardiographic assessment of all patients with hypertrophic cardiomyopathy.

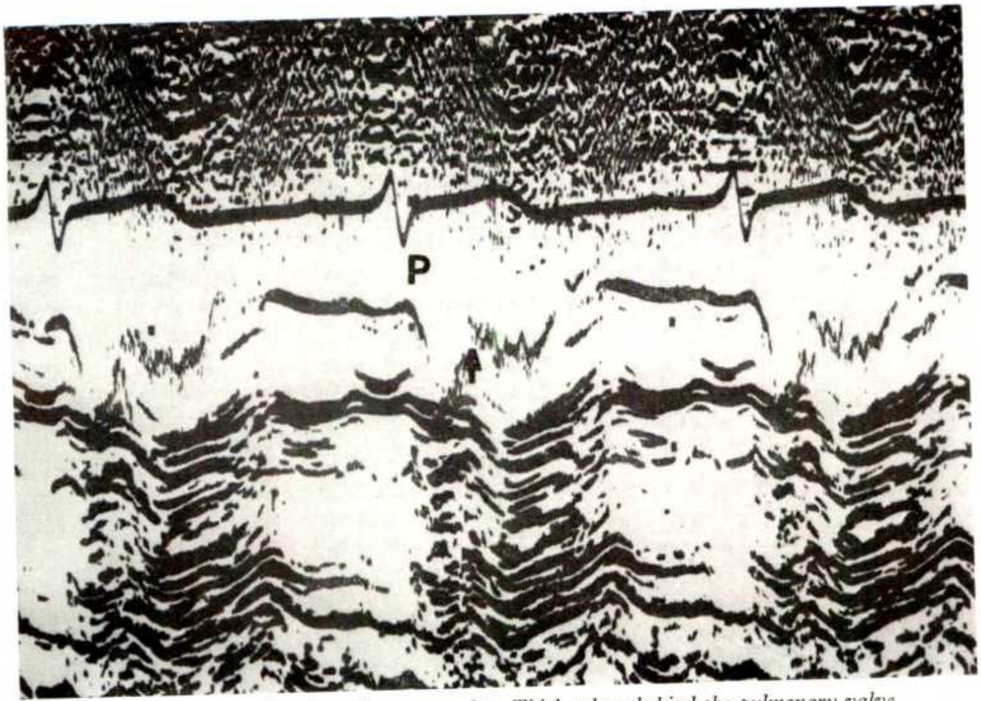

Fig. 2 *Echocardiogram showing pulmonary valve. Thick echoes behind the pulmonary valve produced by infundibulum. Pulmonary cusp (P) with fluttering in systole (arrow) and distinct midsystolic collapse, caused by dynamic subpulmonary stenosis.*

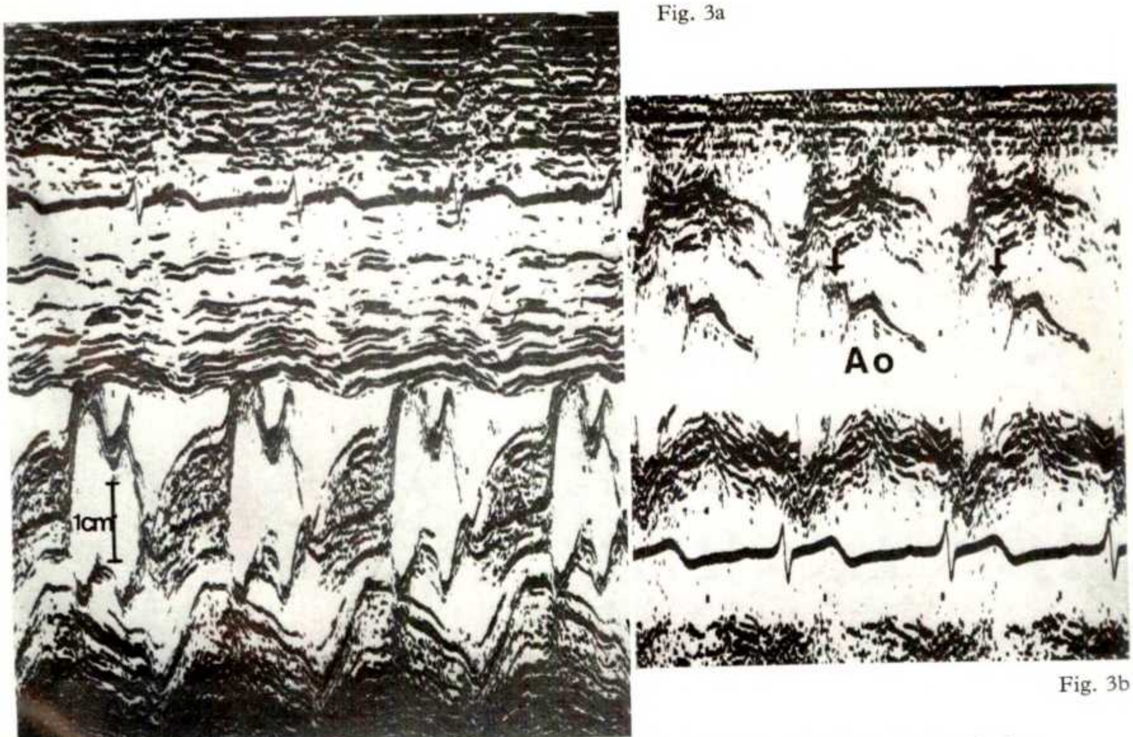

Fig. 3a

Fig. 3b

Fig 3. (*a*) *Echocardiogram showing the ventricular cavities and the mitral valve. There is right ventricular enlargement, with increased thickness of the echoes from the anterior wall, and asymmetric septal hypertrophy. The mitral valve shows an anterior systolic movement.* (*b*) *Echocardiogram showing aortic root with normal opening of the aortic valve cusps in systole and midsystolic collapse (arrows).*

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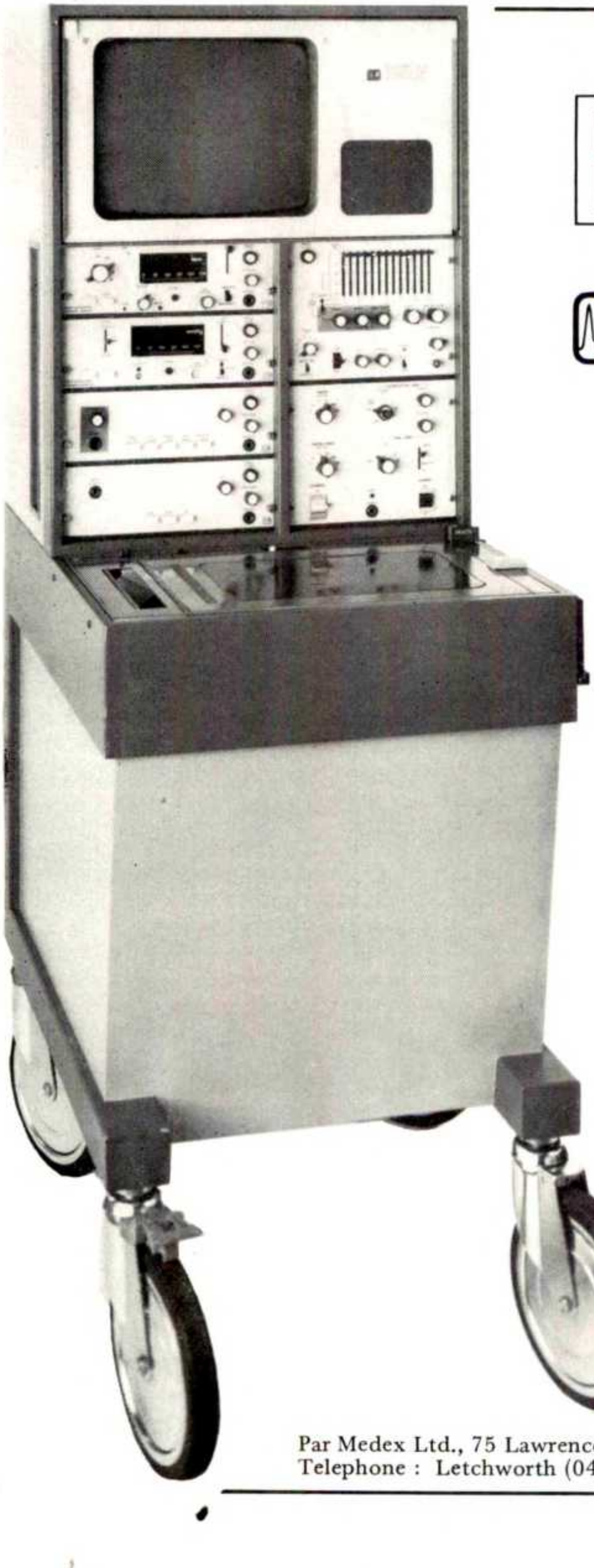

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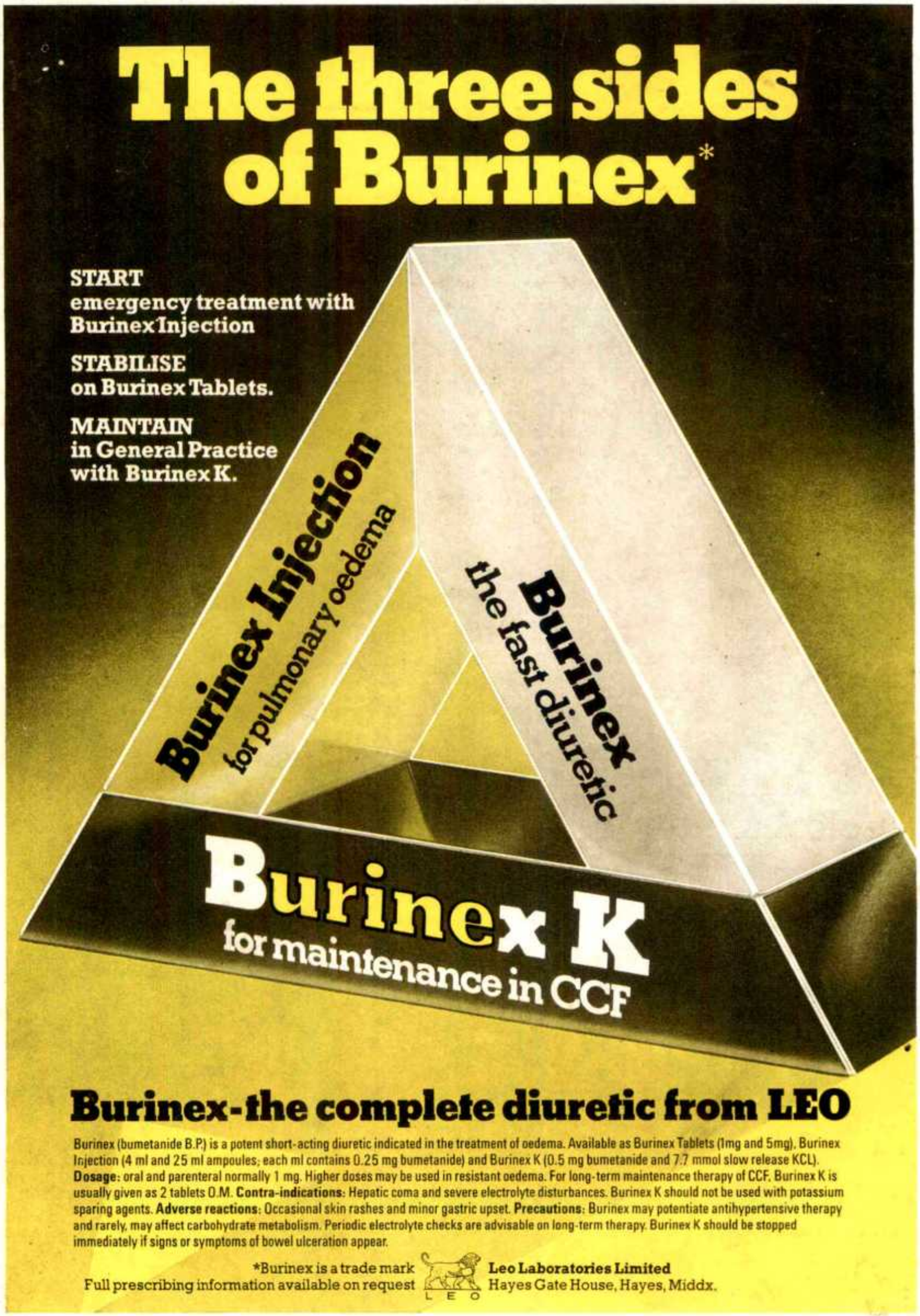

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